INCIDENCE OF PAPILLARY NEOPLASMS OF NERVOUS SYSTEM IN A TERTIARY CARE HOSPITAL. ROLE OF IMMUNOHISTOCHEMISTRY IN THEIR DIFFERENTIAL DIAGNOSIS AND CLASSIFICATION

Dissertation submitted in partial fulfilment of the requirements for the degree of

M.D. (PATHOLOGY)

BRANCH – III

INSTITUTE OF PATHOLOGY AND ELECTRON MICROSCOPY,

MADRAS MEDICAL COLLEGE,

CHENNAI – 600 003.

THE TAMIL NADU
DR. M.G.R. MEDICAL UNIVERSITY
CHENNAI

APRIL 2013

CERTIFICATE

This is to certify that this Dissertation entitled **"INCIDENCE OF PAPILLARY NEOPLASMS OF NERVOUS SYSTEM IN A TERTIARY CARE HOSPITAL. ROLE OF IMMUNOHISTOCHEMISTRY IN THEIR DIFFERENTIAL DIAGNOSIS AND CLASSIFICATION"** is the bonafide original work of Dr.M.YOGAMBAL, in partial fulfilment of the requirement for M.D., (Branch III) in Pathology examination of the Tamilnadu Dr.M.G.R Medical University to be held in April 2013.

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DECLARATION

I **Dr.M.Yogambal,** solemnly declare that the dissertation titled **"INCIDENCE OF PAPILLARY NEOPLASMS OF NERVOUS SYSTEM IN A TERTIARY CARE HOSPITAL. ROLE OF IMMUNOHISTOCHEMISTRY IN THEIR DIFFERENTIAL DIAGNOSIS AND CLASSIFICATION"** is the bonafide work done by me at Institute of Pathology, Madras Medical College under the expert guidance and supervision of **Prof. Dr.SHANTHA RAVISANKAR, M.D., DCP.,** Professor of Neuro Pathology, Institute of Neurology, Madras Medical College. The dissertation is submitted to the Tamilnadu Dr.M.G.R Medical University towards partial fulfilment of requirement for the award of M.D., Degree (Branch III) in Pathology.

Place : Chennai

Date: **Dr.M.YOGAMBAL**

INSTITUTIONAL ETHICS COMMITTEE
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CERTIFICATE OF APPROVAL

To
Dr.M. Yogambal
PG in MD Pathology
Madras Medical College , Ch-3

Dear Dr. M. Yogambal

The Institutional Ethics Committee of Madras Medical College reviewed and discussed your application for approval of the proposal entitled "Incidence of papillary neoplasms of nervous system in a tertiary care hospital. Role of immunohistochemistry in their differential diagnosis and classification" No. 04012011.

The following members of Ethics Committee were present in the meeting held on 28.01.2011 conducted at Madras Medical College, Chennai -3.

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8. Thiru. S. Govindasamy . BA.BL	– Lawyer
9. Tmt. Arnold Soulina	– Social Scientist

We approve the Proposal to be conducted in its presented form.

Sd /. Chairman & Other Members

The Institutional Ethics Committee expects to be informed about the progress of the study, any SAE occurring in the course of the study, any changes in the protocol and patient information / informed consent and asks to be provided a copy of the final report

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ABBREVIATIONS

CPP	:	Choroid plexus papilloma
CPC	:	Choroid plexus carcinoma
PTPR	:	Papillary tumour of pineal region
MPE	:	Myxopapillary ependymoma
GFAP	:	Glial Fibrillary Acidic Protein
CK	:	Cytokeratin
CEA	:	Carcino Embryonic Antigen
EMA	:	Epithelial Membrane Antigen
NSE	:	Neuron Specific Enolase
S-100	:	S-100 protein
ER	:	Estrogen Receptor
PR	:	Progesterone Receptor
WHO	:	World Health Organisation
IHC	:	Immunohistochemistry
PCR	:	Polymerase chain reaction
RT PCR	:	Reverse Transcriptase Polymerase Chain Reaction
ICMR	:	Indian Council of Medical Research
SEER	:	Surveillance, Epidemiology and End Result Program
CBTRUS	:	Central Brain Tumour Registry of the United States
MPNST	:	Malignant peripheral nerve sheath tumour
CNS	:	Central nervous system
IP	:	Incidence Proportion

CONTENTS

INTRODUCTION

- Nervous system neoplasms are common neoplasm affecting both adults and children. The effects of these tumours were devastating even though they constitute a small percentage of all cancers[1]

- Incidence, prevalence and survival rates are important to know the burden of disease among different populations. Over all incidence varies between 9.21 to 18.1 per 100,000 person years in various studies.[2,6,7] Variation in these rates prompted us to find out aetiology, treatment and prognosis of the disease [2].

- As most of the studies done on nervous system tumours were institutional they were prone for bias due to inclusion and exclusion of cases.

- In developed countries like United States, central brain tumour registry of United States (CBTRUS) maintains the brain tumour data from various cancer registries. But in developing countries like India, due to complete lack of registration of newly diagnosed cases, with local registry the exact burden of these tumours goes unnoticed and is under estimated. In these settings multi institutional tertiary care hospital data forms the basis for estimating the disease load.

- There is dire need for descriptive data on primary brain and nervous system tumours as highlighted by Kurland and Schoenberg[3]. Hence this study is contemplated with a view to get descriptive data.

- In contrast to western literature there is no report exclusively available for brain tumours in India.

- Among tumours of the nervous system, those with papillary configuration constitute the vast majority and produces difficulty in diagnosis. Papillary neoplasms of nervous system include both primary central nervous system and spinal cord tumours as well as metastatic papillary tumours.

- Often the histological appearance alone cannot conclude the diagnosis. In difficult cases use of immunohistochemistry aid in differentiating metastasis from primary tumour, histological sub typing and grading. These are needed for the proper treatment and prognostic assessment.

- In this study we analysed the data from our tertiary care hospital to find the epidemiology of papillary neoplasms of nervous system, histopathology, and employed immunohistochemistry to differentiate each tumour.

AIMS AND OBJECTIVES

1. To study the incidence of papillary neoplasms of nervous system.
2. To study the histopathological features with relevance to histological behaviour and grading of papillary tumours.
3. To study the role of immunohistochemistry in their differential diagnosis and classification.
4. To study the immunohistochemical expression in primary nervous system tumours.
5. To study the possible primary sites in nervous system metastatic tumours

REVIEW OF LITERATURE

Papillary neoplasms are a heterogeneous group of neoplasms composed of papillary arrangement of cells with central fibro vascular core. These include both primary and secondary papillary neoplasms. Primary tumours constitute both glial and non glial origin with variable tumour grades.

These tumours include

Primary tumours:

1. Myxopapillary ependymoma
2. Papillary ependymoma
3. Choroid plexus papilloma
4. Atypical choroid plexus papilloma
5. Choroid plexus carcinoma
6. Papillary craniopharyngioma
7. Papillary meningioma
8. Papillary tumour of pineal region
9. Papillary glio neural tumour
10. Astroblastoma
11. Ependymoblastoma

Metastatic tumours:

1. Lung carcinoma
2. Gastro intestinal carcinoma
3. Renal cell carcinoma
4. Ovarian carcinoma
5. Uterine carcinoma
6. Thyroid carcinoma

Epidemiological analysis, histopathological study and grading of these tumours are important for better treatment planning and to assess the prognosis.

* **EPIDEMIOLOGY OF NERVOUS SYSTEM TUMOURS:**

* T.S Surawicz et al [(4)] analysed 20765 central nervous system tumours obtained from CBTRUS during the year of 1990-1994 and concluded that average primary brain tumour incidence was 11.5 per 100,000 person-years. In this study male patients have higher incidence (12.1 per 100,000 person-years) than female patients (11 per 100,000 person-years) which was statistically significant. This study showed whites had higher incidence (11.6 per 100,000 person-years) than blacks (7.8 per 100,000 person-years).

* Faith et al [2] studied the data from Surveillance, Epidemiology and End Result Program (SEER) and CBTRUS during 1973-1999 and highlighted the increase in incidence of brain tumour. In this study they compared the previous study done by Kurland et al., Schoenberg et al., and found out that under reporting and definitional differences were the causes for under ascertainment in these studies.

* Analysis of 54,336 primary central nervous system tumours were done by Arora et al[6] They studied central nervous system tumour epidemiology in England during the period of 1995-2003 and showed an overall incidence of 9.21 per 100,000 person-years with higher incidence in males (9.96 per 100,000 person-years) than females (8.52 per 100,000 person-years) with a male : female ratio of 1.17:1.

* Porter et al [7] studied brain tumour prevalence in United States and found an overall incidence rate of 18.1 per 100,000 person-years for primary brain tumours.

* T.S Surawicz et al [4] showed that meningiomas (24.0%) were the most frequently reported. In this study except meningioma all other nervous system tumours had male predominance and showed an

annual incidence of 7.8 per 100,000 person-years for malignant tumours and 2.1-8.9 per 100,000 person-years for benign tumours.

* Arora et al [6] showed a peak incidence of primary brain tumours in males and females of 75-79 years age group. Patients in the age group of 0-14 years had incidence of 3.56 per 100,000 person-years, those in 15-24years age group had 3.47 per 100,000 person – years incidence, and those in 25-84 years age group had 14.57 per 100,000 person-years incidence.

* Hoffman et al [5] studied 25,258 primary and other central nervous system tumours and documented an increased incidence of all brain tumours with a 1.1% increase over the average annual percentage which was statistically significant. In this study the majority of tumour (53%) occurred in 20-64 year age group; 38% occurred in the elderly (≥65 years) and 9% of the tumour occurred in children.

* Arora et al [6] studied the brain tumour behaviour and showed 60% incidence for malignant tumour, 5.64% for benign tumour and 0.79 – 2.78 for uncertain behaviour. Distribution by site showed that supratentorial and meningeal tumours affect older age group and infra tentorial tumours affect younger patients. Histologically neuro epithelial tumours affect younger patients and unspecified tumours affect older age.

* Data from SEER program and national cancer registry revealed nervous system tumours constitute about 27% of paediatric tumours [8].

* Linabery et al[9], studied the childhood cancer incidence from national cancer institute data during the period of 1992-2004. In this study over all childhood cancer incidence was 158 per 1,000,000 person-years. CNS tumours constitute 27 per 1,000,000 person-years. Male children had higher incidence (29.9 per 1,000,000 person-years) than female children (25.1 per 1,000,000 person-years). Age wise children less than 1 year had an incidence of 30.3 per 1,000,000 person-years. Children between 1-4 years and 5-9 years had an incidence 38.5 and 29.7 respectively. Children between 10-14 years had 25.2 per 1,000,000 person-years incidence. Children between 15-19 years had incidence of 19 per 1,000,000 person-years. Compared to blacks (22.1%) whites had higher incidence (29%). Asian children had an incidence of 20.5 per 1,000,000 person-years.

* A multi institutional study by Jain et al [10] in India showed that paediatric CNS tumours constituted about 14.8% of intra cranial tumours. Among them astrocytomas were the most common tumours.

- **EPIDEMIOLOGY OF NERVOUS SYSTEM METASTASIS:**

* Barnholtz et al [(11)] studied the incidence of brain metastasis during the period of 1973-2001 from the Metropolitan Detroit Cancer Surveillance System and revealed that the percentage of metastases was 9.6%. Among this lung (19.9%) was the most common site for primary, followed by melanoma (6.9%), renal (6.5%), breast (5.1%), and colorectal (1.8%) cancers. The highest incidence proportion %(IP) of brain metastasis occurred at different ages at diagnoses: 40 to 49 years for primary lung cancer; 50- 59 years for primary melanoma, renal, or colorectal cancers; 20 to 39 years for primary breast cancer. Incidence proportion % was significantly increased as Surveillance, Epidemiology and End Result Program stage of primary cancer advanced for all primary sites.

* Smedby et al [(12)], studied brain metastasis in Sweden between 1987 and 2006 and concluded that the annual age-adjusted incidence rate of hospitalisation for brain metastasis doubled from 7 to 14 patients per 100 000 between 1987 and 2006. The most common primary tumours among women were lung (33%), breast (33%) and colorectal cancer (7%), and among men lung cancer (44%), malignant melanoma (12%) and colorectal cancer (9%). The increase was most evident for brain

metastasis patients with lung cancer (both sexes) and breast cancer (women).

* **EPIDEMIOLOGY OF PAPILLARY NEOPLASM OF NERVOUS SYSTEM:**

Even though papillary neoplasms constitute a small percentage in nervous system tumours the descriptive epidemiology is needed for the diagnosis, treatment and assessing the prognosis.

Primary papillary neoplasms:

* **Myxopapillary ependymoma:**
    * The frequency of myxopapillary variant is 9–13 %[13, 14] among all ependymomas. These tumours constitute the most common intramedullary neoplasm. The conus medullaris/ cauda equina region shows an incidence of 0.08 in males and 0.05 per 100 000 persons per year in females [15]. They occur in a wide range of age groups between 6-82 years [16].
    * Cervoni et al [17] studied 320 filum terminale ependymomas. In this 83% were of myxopapillary type, with a male: female ratio 2.2:1.
* **Papillary ependymoma**
    * Based on Central Brain Tumour Registry of the United States (2006) ependymomas have 0.22-0.29 per 100,000

person-years incidence[15]. This incidence is mainly affected by location and histological type. As per WHO the incidence of papillary ependymoma statistics was not available.

* **Choroid plexus tumours:**

  * Choroid plexus tumours consist of choroid plexus papilloma, atypical choroid plexus papilloma, and choroid plexus carcinoma. Among all brain tumours these tumours constitute about 0.3-0.6%. However they represent 2-4% of nervous system tumours in children <15 years, and 10-20 % in those occurring in 1st year of life.

  * As per Janisch et al, Rickert et al, and Wolff et al the approximate annual incidence of these tumours was 0.3 per 1,000,000 populations per year.[18,19,20]. Male: female ratio was1.2:1. Approximately 80% of lateral ventricular tumours occur in less than 20 years age group, whereas 4th ventricle tumours were equally distributed in all age groups.

  * As per Janisch W et al, Strojan P et al [18,21] study most common site for CPP and CPC was lateral ventricle (50%) followed by third ventricle (5%), and fourth ventricle (40%).

* **Papillary craniopharyngioma:**

* As per Bunin GR et al, [22] craniopharyngioma constitute 1.2-4.6% of all intracranial tumours. They account for 0.5-2.5 new cases per 1,000,000 population per year and 5-10% 0f intracranial tumours in children.[23] In children these tumour were the most common non-neuroepithelial intracerebral neoplasms.

* Papillary craniopharyngioma [23, 24] occurs exclusively in adults with a mean age of 40-45 years with no sex predilection. Suprasellar is the most common site. Koral et al, noted unusual locations like sphenoid sinus.[25]

*** Papillary meningioma:**

***** As per Claus et al [26] 24-30% of intracranial tumours were meningiomas in USA and average annual incidence ranged up to 13 per 100,000 population in Italy. Middle aged and elderly people were the most commonly affected people with peak during the 6^{th} and 7^{th} decades. [27] Middle aged females showed a higher incidence with female: male ratio 1.7:1. Jasskelainen et al[28] analysed and found a male predominance in atypical and anaplastic meningiomas. As

per WHO the exact frequency of papillary meningioma was not available because of its rarity.

* **Papillary tumour of pineal region (PTPR):**

  * In the pineal region it is a rare neoplasm of adults. Jouvet et al[(76)] studied a series of 6 cases with similar histology and described PTPR in 2003. Since these tumours were rare, incidence data were not available. In this sex predilection was not noted and the age group was 5-66 years with mean age of 32 years.

* **Papillary glioneuronal tumour:**

  * Komori et al, [(29)] described this different clinicopathologic entity in 1998. As per WHO, population based epidemiological data was not available for this tumour. Only several case reports were available for this tumour.[(30,31)] These tumours have a wide age range and they do not have gender predilection

.

* **Other uncommon papillary tumours:**

* Astroblastoma a rare glial tumour mostly affecting children, young adults, and adolescents. These are very unusual neoplasm and no uniform criteria applicable for diagnostic purpose. So no definitive epidemiological data available [(32)]. As per WHO 40 cases in three series analysed and found that median age was 11 years with range of 1-58 years. Among these all affected patients were females, suggesting a female preponderance.
* Medulloepithelioma a malignant embryonal rare brain tumour occurring in young children between 6 months-5 years with 50% cases affecting first two years[(33)]. Age at presentation ranged from <1 month – 23 years in 37 published cases with equal male: female ratio. [(33,34,35,36)]

* **Metastatic papillary tumours of nervous system:**
  * In nervous system tumours metastatic tumours were the most common tumours with up to 11 per 100,000 population per year probably under diagnosed and underestimating the true incidence[(37)].
  * Gavrilovic et al[(38)] autopsy study revealed that 25% of patients who die of cancer had brain metastases.

* As per Stone et al and Donadey et al [39,40] 4-15% patients with solid cancer had leptomeningeal metastasis and 8-9% of patients had leptomeningeal and dural metastasis respectively.
* Mut et al[41] studied spinal and intramedullary metastasis and concluded that 5-10% of all patients with cancer had frequent spinal and intramedullary metastasis.
* As per Suki et al,[37] <25 years age group people have <1 per 100,000 incidence, and greater than 30 per 100,000 at age of 60 years.
* Khan et al study[42] showed that brain metastasis occur in 30% of adults and 6-10 % of children with cancer.
* Most common metastasis with papillary pattern are
    - Lung carcinoma
    - GIT malignancy
    - Breast carcinoma
    - Papillary carcinoma thyroid
    - Papillary renal cell carcinoma
    - Female Genital Tract carcinoma with papillary architecture
    - Male genito urinary tract malignancy

- Head and Neck malignancy

HISTO MORPHOLOGY OF PAPILLARY TUMOUS:

❖ Primary papillary tumours:

- Myxopapillary ependymomas are WHO GRADE 1 tumour. Grossly these are encapsulated, lobulated and soft in consistency and greyish in colour.
- Histologically these tumours are composed of cuboidal to columnar cells arranged in a papillary manner around the vascular core. In between the blood vessels and tumour cells, abundant myxoid material accumulates which shows alcian blue positivity.
- Papillary ependymomas are WHO grade II tumours. Grossly they appear soft tan tumours with well demarcated borders. In histology they are formed by single layer of cuboidal tumour cells forming papillae. Perivascular arrangement is also seen. These cuboidal tumour cells show smooth contiguous surface.[43]
- Choroid plexus papillomas (WHO grade I tumour) are circumscribed and cauliflower like masses which is usually well demarcated from the adjacent brain tissue.

Histologically they have papillary pattern with central delicate fibro vascular core. These cores are lined by uniform single layer of cuboidal to columnar cells. Cells have oval to round, basally situated uniform nuclei. They have very low mitotic activity.

- Aquiline et al, Buccoliero et al, Sarkar et al [44,45,46] studied choroid plexus papilloma and found out unusual histologies including mucinous degeneration, oncocytic change and melanisation, as well as degenerative change including xanthomatous degeneration, cartilage, bone and adipose tissue formation.
- Atypical choroid plexus papilloma (WHO grade II) is defined as choroid plexus papilloma with increased mitotic activity.
- Jeibmann et al[47] study showed that a mitotic index of 2 or more per 10 randomly selected high power fields can be used to diagnose atypical CPP. This study also established that up to 2 of the following 4 features may be present- 1) increased cellularity, 2) blurring of papillary pattern, 3) nuclear plemorphism, 4) area of necrosis but these features are not necessary to diagnose atypical CPP.

- Choroid plexus carcinoma is WHO grade III tumour with invasive borders that may appear haemorrhagic, solid and necrotic.
- Histologically CPC shows signs of malignancy. As per one study, signs of malignancy included at least 4 of the following 5 features-

  1) Frequent mitoses (>5 per 10 HPF),

  2) Increased cellularity,

  3) Blurring of papillary pattern,

  4) Nuclear plemorphism,

  5) Necrotic areas
- CPC can mimic as metastatic carcinoma. Therefore various immunostains are needed for a conclusive opinion.
- Papillary craniopharyngioma is WHO grade I tumour. Grossly these are solid well circumscribed tumours which shows absence of calcification and cholesterol-rich machinery oil like material. Histologically these tumours have well differentiated monomorphous squamous epithelium lacking surface maturation. These tumours also have wet keratin and picket-fence like palisades.

- Papillary meningioma is a WHO grade III tumour. Grossly they are firm, rubbery and rounded masses with dural attachment. These tumours have perivascular papillary pattern.
- Ludwin et al, Kros et al, Pasquier et al[48,49,50] studied the aggressive nature of this tumour and found that invasion of brain and local invasion was seen in 75% of cases, metastases in 20%, and recurrence in 55% and death in roughly half.
- Papillary tumour of pineal region corresponds to WHO grade II or III, but histological grading remain to be defined. These are well defined tumours grossly. Histologically this is an epithelial – appearing tumour which shows papillary pattern sometimes exhibiting ependymal like differentiation. The papillae are lined by large, pale to eosinophilic columnar cells.
- Papillary glioneuronal tumours are indolent tumours which behave like a WHO grade I tumour but biologic progression has been reported in rare cases. Grossly it is a variably solid or cystic tumour. They show papillary and pseudo papillary

pattern lined by single or pseudo stratified cells with round nuclei. Focal collection of ganglion cells can be seen[51]

- Astroblastomas show variable biologic behaviour. In this sufficient data is not available and so WHO grading has not been done. Grossly the tumour is grey- pink to tan in colour with foci of necrosis and haemorrhage. Tumour cells are arranged in papillary pattern showing unipolar cytoplasmic processes which connect the neoplastic cells to stromal blood vessels.

❖ **HISTOMORPHOLOGY OF METASTATIC PAPILLARY TUMOURS:**

- Metastasis to brain and spinal cord often produce grossly rounded, circumscribed, grey white to tan masses, most of them showing central necrosis with surrounding edema.
- Collection of mucoid material can be seen in metastatic adenocarcinomas.
- Histologically secondary nervous system tumours are very diverse as in primary tumours. Immunostains are needed for primary identification in unknown primary cases.

- **ROLE OF IMMUNOHISTOCHEMISTRY IN NERVOUS SYSTEM TUMOURS:**

  - Diagnostic neuropathology has improved more in recent past due to advance in immunohistochemistry based techniques. Newer reagents are continuously being developed against specific antigens associated with stages of cell lineage, oncogene, cell cycle and suppressor gene product or cell activation. Use of these antibodies will help us to define

    1) Nature of cellular maturation,

    2) Tissue differentiation

    3) Tumour progression

    4) Metastasis.

  - The continuing refinement and evolution of reagents and use of newer techniques result in tremendous improvement of histological classification. They are mainly used in difficult cases and in cases of unknown primary cases.

  - Immunohistochemistry helps not only to know about the ability of the tissue to express a particular antigen but also its exact cellular localization. This method also employs different antibodies to distinguish the antigenic differences between the cells. These antigenic differences can identify

a. Specific cellular lineage

b. Functional differences between the cells

c. Different subpopulation within one cell lineage

d. Identify infections.

- The tremendous progress in the field of immunohistochemistry allows the exploration of the molecular phenotypes of the developing CNS tumours.

The most common methods used for immunohistochemistry are :

1) Peroxidase – antiperoxidase method

2) Avidin-biotin method

- The main key requisite to this diagnostic modality is antibody specific to particular antigen.
- The most important groups of antibodies are

1. Intermediate filaments

2. Neuroendocrine related proteins

3. Markers with predominant expression in CNS tumour

4. Markers associated with suppressor genes, oncogenes and related gene products

5. Markers to detect cell proliferation and cell death in CNS tumours

6. Markers of historical significance and

Intermediate filaments:

The intermediate filament proteins are intercellular filaments which measures about 10micrometer in diameter and forms an important component of the cytoskeleton.

There are 6 classes of intermediate filament proteins.

1) Keratin - identifies epithelium

2) Vimentin – identifies

- Mesenchymal cells
- Astrocytes
- Primitive neuroepithelial cells
- Developing neuron

3) Glial fibrillary acidic protein (GFAP) identifies

- Astrocytes
- Nonmyelinating Schwann cells

- Ependymal cells
- Peripherin identifies - neurones of CNS and peripheral nervous system

Of these intermediate filaments, keratin, Vimentin and Glial fibrillary acidic protein are used for routine immunohistochemistry.

Vimentin is most widely expressed antigen in a variety of mature tissues and embryonic tissue. It is a 57-kD protein which was first isolated from a mouse fibroblast culture. In Latin vimentum means describing an array of flexible rods from which its name was derived. This protein is considered to be the main member of the intermediate filament family. Most of the time, when 2 or more IFPs are co expressed by a cell line or neoplasm, Vimentin is almost always one of them which is not considered to be cell type-specific. Positivity of vimentin denotes presence of antigen within the cells.

- **Glial fibrillary acidic protein (GFAP)** is a useful marker for nervous system astroglial cells. This 51-kD protein is the major component of astrocytes and ependymal cells which is not expressed by mature oligodendroglial cells.
- Firstly it is not specific for astroglial cells.
- Secondly there is considerable interlaboratory variation.

- Third problem is that the neoplastic astroglial cell and an entrapped reactive one cannot be differentiated.
- Fourth, there is no reliable correlation between the degree of GFAP expression and the tumour anaplasia.
- **Cytokeratins (CK)** are the most common intermediate filament. It is a marker of epithelium and its neoplasms. In CNS, it differentiates primary high-grade tumour from poorly differentiated metastatic carcinoma and also seen in chordomas, meningiomas, gliosarcomas, many astrocytomas, and oligodendrogliomas.
- **Carcino embryonic antigen (CEA)** is a 180-kD glycoprotein. Adenocarcinomas of the lung, colon, stomach, pancreas, biliary tree, urinary bladder, paranasal sinuses, endocervix, sweat glands, and breast are typically positive for CEA antibodies. Adenocarcinomas of prostate, kidney, endometrium, adrenal gland along with mesothelioma and serous ovarian tumors essentially negative for CEA antibody.
- **Epithelial membrane antigen (EMA)** is eencoded by the MUC1 gene on chromosome 1. Epithelial membrane antigen is a transmembrane glycoprotein of the breast mucin complex. Its expression is increased in carcinomas [81, 82]. The use of EMA

antibody is in the detection of epithelial differentiation, as a supplement to the cytokeratins.

- So, to differentiate between a primary and a secondary CNS tumour, the antibody panel should have CK, CEA and GFAP.

Neuroendocrine related proteins:

Two proteins are rather consistently expressed by the neuroendocrine lineage

a. Neuron specific enolase
b. Synaptophysin
c. Chromogranin.

A. **Neuron specific enolase** is one of the first markers for neuroendocrine system, but extensive cross reaction of Gamma-subunit with the Beta-subunit of NSE in many non-neuroendocrine cells limits the advantages of this antibody.

B. **Synaptophysin** is major calcium – binding protein present in the synaptic-vesicle membrane and it cross-reacts with other granule associated proteins. It is demonstrated in Medulloblastomas, neurocytomas, gangliogliomas, pineocytomas, ganglioneuromas and some oligodendrogliomas. Many peripheral neuroendocrine

tumours like pheochromocytoma, small cell carcinoma of lung, carcinoid and pituitary adenomas also express this antigen.

C. **Chromogranin A** is expressed by dense-core vesicles of neuroendocrine cells. Most neuroendocrine tumours outside CNS express this antigen. In CNS only ganglioglioma consistently expresses this antigen. These are expressed in retinoblastoma and medulloblastoma with variable intensity.

Germ cell tumour markers:

Germ cell tumours are not uncommon in central nervous system. The primordial germ cell disseminates most frequently from mediastinum and diencephalopineal region. The germ cell tumour markers used in CNS tumours are

1) Alpha feto protein – AFP

2) Placental alkaline phosphatase – PLAP

3) Beta Human chorionic gonadotrophin – BHCG

More over Cytokeratin, Epithelial membrane antigen (EMA) and Vimentin are often needed.

Miscellaneous markers:

S-100 protein: This is first isolated from CNS in 1965. It is localized in the cytoplasm and nucleus of astrocytes, oligodendrocytes and Schwann cells. Few neurons also have this protein. Its use is rather limited by the vastness of its neural positivity. The main use is in identifying MPNST from therapeutic application in out so far future.

The tumour markers are very important diagnostic tools even though they have many pitfalls which one should be aware of. The interpretation of immunohistochemistry results should always be done in correlation with the morphology, proper clinical and radiological history.

The future of immunohistochemistry is aimed at not only for the diagnosis and prognostication of the tumours but also being able to analyse and predict upon the probable response to various chemotherapeutic agents.

ROLE OF IMMUNOHISTOCHEMISTRY IN PAPILLARY NEOPLASMS:

- **Primary papillary tumours:**
- **Myxopapillary ependymoma:**
- Myxopapillary ependymoma shows GFAP, Vimentin and S-100 positivity but cytokeratin reactivity is absent.

- Coffin et al[52] studied the tumours to be distinguished from myxopapillary ependymoma. These include myxoid chondrosarcoma, mesothelioma, chordoma, and papillary adenocarcinoma. In this cytokeratin negativity and GFAP positivity will confirm the diagnosis.
- Ang et al[53] studied 25 cases of papillary tumours in those 2 cases of myxopapillary ependymoma showed GFAP and Vimentin positivity.
- Two cases of myxopapillary ependymoma in Mannoj et al[54] study showed GFAP positivity and CK negative.
- **Papillary ependymoma:**
- Papillary ependymomas show GFAP positivity and Nestin positivity. EMA and CK are negative.
- 4 cases of papillary ependymoma in a study by Ang et al[53] showed GFAP, S-100 and Vimentin positivity in all 4 cases.
- Mannoj et al[54] studied in 4 cases of papillary ependymoma two tumours showed CK positivity. This positive staining was observed in apical part.
- **Choroid plexus tumours:**
- In choroid plexus papilloma cytokeratin and Vimentin are expressed in all cases. 55-90% of cases are S-100 positive. GFAP

is absent in normal choroid plexus epithelium but 22-55% of CPP shows positivity. In this 74% of CPP showed CK 7positivity and CK 20 negativity.[55]

- Hasselblatt et al[56] studied choroid plexus tumours and found out that transthyretin was positive in 70% of CPP.
- Ang et al[53] showed that in 5 cases of choroid plexus papilloma all 5 showed CK positivity, 4 showed S-100 positivity and 2 cases showed focal GFAP positivity. 1 case of choroid plexus carcinoma studied showed CK, S-100 positivity and focal GFAP positivity.
- In a study by Mannoj et al[54] CPP cases showed CK-positivity. 3 cases were GFAP positive. In CPC solid, areas were negative for CK.
- **Papillary craniopharyngioma:**
- In contrast to adamantinomatous variant of raniopharyngioma, papillary variant does not show beta catenin mutation.
- **Papillary meningioma:**
- All meningiomas show Vimentin positivity.EMA is also positive in majority of the meningiomas.
- In study by Ang et al[53], papillary meningioma showed only Vimentin positivity.

- **Other papillary tumours:**
- Papillary tumour of pineal region showed CK positivity and focal GFAP, S-100 and Vimentin positivity.
- Astroblastomas were positive for Vimentin, GFAP and S-100. They are negative for CK.
- **Metastatic papillary tumours:**
- Immunohistochemistry is very useful in identification of unknown primary. Some of the primary CNS tumours like CPC can produce difficulty in diagnosis. In histology they mimic metastatic deposits. In these settings IHC is needed

    1) To differentiate primary tumour from metastasis
    2) To identify the primary site in metastasis

- No single immunostain is useful. So use of antibody panel is needed to identify the primary.
- Ang et al[53] studied 25 papillary neoplasms of nervous system. In this metastatic papillary adenocarcinoma comprised 7 cases. They used a panel of antibodies (GFAP, S-100, CEA, CK, VM, prealbumin). All 7 metastatic tumours showed strong cytoplasmic CK staining. 6 cases showed CEA positivity. None of the primary tumours showed CEA positivity.

- In our study we used GFAP, Vimentin, S-100, EMA, CEA, Pancytokeratin, thyroglobulin, ER,PR,NSE for identification of primary papillary tumour origin and to differentiate primary papillary tumour from papillary metastases.

MATERIALS AND METHODS

This study is a retrospective- cum- prospective descriptive study of papillary neoplasms of nervous system conducted in Department of Neuropathology, Madras Medical College and Rajiv Gandhi Government General hospital, Chennai during the period of January 2007 to December 2011.

Source of data:

- The papillary neoplasms reported in Department of Neuropathology, Madras Medical College during the period of January 2007 to December 2011 from the Department of Neurosurgery, Rajiv Gandhi Government General hospital. A total 62 papillary tumour neurosurgical specimens were received during the study period.

Inclusion Criteria:

- All the nervous system neoplasms showing papillary pattern irrespective of their origin whether it is primary or secondary.

Exclusion criteria:

1. Recurrent papillary tumours
2. Non neoplastic conditions

3. Cases with inadequate material from the tumour for doing both H&E and immunohistochemistry

METHOD OF DATA COLLECTION:

- Detailed history of the cases regarding age, sex, symptoms, laterality of symptoms, radiological findings, history of previous surgery for the same symptoms, details of gross characteristics were obtained for all the 62 neoplasms with papillary pattern from Surgical Pathology records from neuropathology. Freshly cut sections and Hematoxylin Eosin stained 4 µ thick sections of the paraffin tissue blocks of this specimens were reviewed and graded using the WHO grading criteria. (Annexure II). Out of 62 cases blocks were available for 56 cases of papillary neoplasms. All the 56 cases were selected from the total cases and their representative formalin fixed paraffin embedded tissue samples were subjected to Immunohistochemistry with a panel of 6 markers and 2 to 3 additional markers. The results were recorded with photographs. Follow up data of some of the patients regarding the adjuvant therapy, recurrence, disease free survival were obtained from

Medical Records Section of Department of Oncology and neurosurgery

IMMUNOHISTOCHEMICAL EVALUATION:

- Immunohistochemical analysis using panel of markers including pan cytokeratin, Glial Fibrillary Acidic Protein, S-100 protein, Vimentin, carcino embryonic antigen and Epithelial membrane antigen were done in paraffin embedded tissue samples using Supersentive polymer HRP system based on non biotin polymeric technology. Due to economic constraints, immunohistochemistry for secondary metastatic deposits were done only in selected cases to identify the origin of primary. Thyroglobulin, estrogen receptor and progesterone receptor were the additional markers used in this study to identify the primary.

- Sections with a thickness of 4 µ from selected formalin fixed paraffin embedded tissue samples were transferred onto gelatin coated slides. Heat induced antigen retrieval was done. The antigen is bound with mouse monoclonal antibody (Biogenex) against pan cytokeratin, Glial Fibrillary Acidic Protein, S-100 protein, Vimentin, carcino embryonic antigen, Epithelial membrane antigen, Thyroglobulin, estrogen receptor and progesterone

receptor and then detected by the addition of secondary antibody conjugated with horse radish Peroxidase-polymer and Diaminobenzidine substrate

ANTIBODIES FOR IHC

Antigen	Vendor	Species	Dilution	Positive control
Pan cytokeratin	BIOGENEX	Mouse	Ready to use	Skin
Glial Fibrillary Acidic Protein	BIOGENEX	Mouse	Ready to use	Normal Brain parenchyma
S-100	BIOGENEX	Mouse	Ready to use	Skin
Vimentin	BIOGENEX	Mouse	Ready to use	Uterus
Carcino Embryonic Antigen	BIOGENEX	Mouse	Ready to use	Colon
Epithelial Membrane Antigen	BIOGENEX	Mouse	Ready to use	Kidney
Thyroglobulin	BIOGENEX	Mouse	Ready to use	Thyroid
Estrogen receptor	BIOGENEX	Mouse	Ready to use	Breast
Progesterone receptor	BIOGENEX	Mouse	Ready to use	Breast

The step by step Immunohistochemistry procedure was given below in detail.

PREPARATION OF SLIDES:

1. Sections with a thickness of 4 µ were cut from formalin fixed paraffin embedded tissue samples and transferred to gelatin-chrome alum coated slides.
2. The slides were incubated at 58ºC for overnight.
3. The sections were deparaffinised in xylene for 15 minutes x 2 changes.
4. The sections were dehydrated with absolute alcohol for 5 minutes x 2 changes.
5. The sections were washed in tap water for 10 minutes.
6. The slides were then immersed in distilled water for 5 minutes.

ANTIGEN RETRIEVAL:

7. Heat induced antigen retrieval was done with microwave oven in appropriate temperature with appropriate buffer for 20 to 25 minutes.
8. The slides were then cooled to room temperature and washed in running tap water for 5 minutes.

9. The slides were then rinsed in distilled water for 5 minutes.
10. They were washed with appropriate wash buffer (phosphate buffer) for 5 minutes x 2 changes.
11. Peroxidase block was applied over the sections for 10 minutes.
12. The slides were washed in phosphate buffer for 5 minutes x 2 changes.
13. Sections were covered with power block for 15 minutes.

ANTIBODY APPLICATION:

14. The sections were drained (without washing) and appropriate primary antibody was applied over the sections and incubated for 45 minutes.
15. The slides were washed in phosphate buffer for 5 minutes x 2 changes.
16. The slides were covered with Super Enhancer for 30 minutes.
17. The slides were washed in phosphate buffer for 5 minutes x 2 changes.
18. The slides were covered with SS Label for 30 minutes.
19. The slides were washed in phosphate buffer for 5 minutes x 2 changes.

CHROMOGEN APPLICATION:

20. DAB substrate was prepared by diluting 1 drop of DAB chromogen to 1 ml of DAB buffer.
21. DAB substrate solution was applied on the sections for 8 minutes.
22. The slides were washed in phosphate buffer solution for 5 minutes x 2 changes.
23. The slides were washed well in running tap water for 5 minutes.
24. The sections were counterstained with Hematoxylin stain for 2 seconds (1 dip).
25. The slides were washed in running tap water for 3 minutes.
26. The slides were air dried, cleared with xylene and mounted with DPX.

INTERPRETATION & SCORING SYSTEM:

- The immunohistochemically stained slides were analyzed for the presence of reaction, cellular localization (nuclear /cytoplasmic /membranous), percentage of cells stained and intensity of reaction. In this study IHC staining was graded by using semi quantitative scale ranging from 0 (no immunoreactive cells) to 4+ (75-100% of the neoplastic cells are immunostained) The symbols 1+, 2+, and

3+ refer to the immunostaining of up to 25%, 25-50%, and 50-75% of the neoplastic cells, respectively[67]

* **STATISTICAL ANALYSIS:**

- The statistical analysis is performed using statistical package for social science software version 11.5. Expression of each marker indicates the cell of origin in primary and secondary tumours.

OBSERVATION AND RESULTS

In the study period of 5years from January 2007 to December 2011, a total of 2932 specimens were received in the Neuropathology department, Madras Medical College for histological examination. Total numbers of neoplasms received were 2333;of these tumours with papillary pattern accounted for 62 cases with a percentage of 2.66 %. The total number of non neoplastic cases was 593. The ratio of neoplastic and non neoplastic cases was 4.3:1. Metastatic papillary tumours are the most common nervous system tumour with papillary pattern. Out of 62 cases metastasis constituted 39 cases (62.90%) In this study primary nervous system tumours with papillary pattern constituted 23 cases (37.10%). (Table 1 Chart 1)

TABLE - 1

ORIGIN-WISE DISTRIBUTION OF NERVOUS SYSTEM NEOPLASMS WITH PAPILLARY PATTERN

S.no	Origin	Number of cases	Percentage
1	Primary	23	37.10%
2	Secondary	39	62.90%
3	Total cases	62	100%

0-10 yrs was the most common age group for the primary papillary neoplasms in this study. Out of 23 cases 0 to 10 year age group constituted 7 cases with relative percentage of about 11.29% among overall papillary tumours, and 30.44% among primary papillary tumours. Next most common age group was 11 to 20 years which included 6 cases with a relative percentage of 9.68% among papillary tumours and 26.09% among primary papillary tumours. Least common age group was 4^{th} to 7^{th} decade which included 3 cases with a relative percentage of 4.84% overall and 13.04% among primary papillary tumours. The age wise distribution of primary papillary tumours is shown in this table. (Table 2 Chart 2)

TABLE – 2

AGE-WISE DISTRIBUTION OF PRIMARY PAPILLARY TUMOURS OF NERVOUS SYSTEM

S. no	Age in years (primary)	Number of cases	% (among primary papillary tumours)	% (overall)
1	0 to 10	7	30.44%	11.29%
2	11 to 20	6	26.09%	9.68%
3	21 to 30	4	17.39%	6.45%
4	31 to 40	3	13.04%	4.84%
5	41 to 50	0	0	0
6	51 to 60	3	13.04%	4.84%
7	61 to 70	0	0	0
8	Total cases	23	100%	37.10%

Metastatic tumours are most common in 3rd to 6th decade with peak age group between 51 to 60 years which constitutes about 13 cases with relative percentage of 20.97% among overall papillary tumours of nervous system, 33.33% among secondary deposits with papillary pattern. Least common age groups are 1st two decades (0%). Age wise distribution of metastatic tumours with papillary pattern is shown in this table. (Table 3 chart 3)

TABLE – 3

AGE WISE DISTRIBUTION OF METASTATIC PAPILLARY TUMOURS OF NERVOUS SYSTEM

S.no	Age in years	Number of cases	Percentage (2* papillary tumours)	Percentage (Overall)
1	0 to 10	0	0	0
2	11 to 20	0	0	0
3	21 to 30	3	7.69%	4.83%
4	31 to 40	6	15.38%	9.68%
5	41 to 50	11	28.22%	17.74%
6	51 to 60	13	33.33%	20.97%
7	61 to 70	6	15.38%	9.68%
8	Total cases	39	100%	62.90%

Males are most commonly affected in primary and secondary nervous system tumours with relative overall percentage of 27.42% in primary tumours, 38.71% in secondary tumours. Male : Female ratio for papillary tumour was 2:1.This table shows sex wise distribution of primary and secondary papillary tumours of nervous system. (Table 4 and Chart 4), (Table 5 and Chart 5)

TABLE – 4

SEX WISE DISTRIBUTION OF PRIMARY PAPILLARY TUMOURS NERVOUS SYSTEM

S.no	Sex (Primary)	Number of cases	% (Among 1* papillary tumours)	% (Overall)
1	Male	17	73.91%	27.42%
2	Female	6	26.09%	9.68%
3	Total cases	23	100%	37.10%

TABLE – 5

SEX WISE DISTRIBUTION OF METASTATIC PAPILLARY TUMOURS OF NERVOUS SYSTEM

S.no	Sex (Secondary)	Number of cases	% (Among 2* papillary tumours)	% (Overall)
1	Male	24	61.54%	38.71%
2	Female	15	38.46%	24.19%
3	Total cases	39	100%	62.90%

In this study the most common site for primary papillary tumour was spinal cord which constituted about 9 cases (overall 14.52%) with relative percentage of about 39.12% among primary papillary tumours. Other common sites were lateral ventricle and cerebrum each constituting 4 cases (6.45%). Sellar region was the least common site (3.22%) with an incidence 8.70% among primary tumours. Site wise distributions of primary papillary tumours are shown in this table. (Table 6 Chart 6).

TABLE – 6

SITE WISE DISTRIBUTION OF PRIMARY PAPILLARY TUMOURS OF NERVOUS SYSTEM

S.no	Site (primary)	Number of cases	% (Among 1* papillary tumours)	% (Overall)
1	Cerebrum	4	17.39%	6.45%
2	Posterior fossa	2	8.70%	3.23%
3	Lateral ventricle	4	17.39%	6.45%
4	Third ventricle	2	8.70%	3.22%
5	Spinal cord	9	39.12%	14.52%
6	Sellar	2	8.705	3.23%
7	Total cases	23	100%	37.10%

In this study cerebrum was the most common site for metastatic deposits with papillary pattern which constituted 29 cases with overall percentage of 46.77% and 74.36% among secondary tumours. Least common site was ventricles (0%). The site of distribution of metastatic deposits with papillary pattern is shown in this table. (Table 7 Chart 7).

TABLE – 7

SITE WISE DISTRIBUTION OF METASTATIC DEPOSITS IN NERVOUS SYSTEM WITH PAPILLARY PATTERN

S.no	Site (Secondary)	Number of cases	% (Among 2* papillary tumours	% (Overall)
1	Cerebrum	29	74.36%	46.77%
2	Posterior fossa	7	17.95%	11.3%
3	Lateral ventricle	0	0	0
4	Third ventricle	0	0	0
5	Spinal cord	3	7.69%	4.83%
6	Sellar	0	0	0
7	Total cases	39	100%	62.90%

In cerebrum, the frontal lobe was the most common site for secondary deposits with papillary pattern which constituting 13 cases (44.83%). Temporo parietal region was the next common site (24.14%). Lobe wise distributions of metastatic deposits with papillary pattern are shown in this table. (Table 8 and Chart 8)

TABLE – 8

CEREBRAL LOBE WISE DISTRIBUTION OF METASTATIC TUMOUR WITH PAPILLARY PATTERN

S.no	Lobes of cerebrum (secondary)	Number of cases	Percentage
1	Frontal	13	44.83%
2	Temporal	2	6.90%
3	Parietal	2	6.90%
4	Temporo parietal	7	24.14%
5	Parieto occipital	5	17.24%
6	Total cases	29	100%

Histomorphological wise, metastatic papillary adenocarcinomatous deposit was the most common type which constituted about 39 cases (62.90%). Among primary papillary tumours, myxopapillary ependymoma constituted 7cases (8.06%). Histomorphological distributions of tumours with papillary pattern are shown in this table. (Table 9 Chart 9).

TABLE – 9

HISTOMORPHOLOGICAL DISTRIBUTION OF NERVOUS SYSTEM TUMOURS WITH PAPILLARY PATTERN

S.no	Histomorphology	Number of cases	Percentage
1	Metastatic papillary adeno carcinomatous deposits	39	62.90%
2	Myxopapillary ependymoma	7	11.29%
3	Papillary meningioma	5	8.06%
4	Choroid plexus papilloma	2	3.23%
5	Choroid plexus papilloma with atypia	2	3.23%
6	Choroid plexus carcinoma	2	3.23%
7	Papillary craniopharyngioma	2	3.23%
8	Others	3	4.83%
9	Total cases	62	100%

In this study the primary site for metastatic deposits with papillary pattern was known for 29 cases. Lung was the primary site for 20 cases (51.28%). Next was thyroid and included 4 cases (10.26%). 10 cases (25.64%) were unknown primary when presented with metastasis or details were not available. (Table 10 Chart 10)

TABLE – 10

PRIMARY TUMOUR WISE DISTRIBUTION OF METASTATIC DEPOSITS WITH PAPILLARY PATTERN

S.no	Primary tumour	Number of cases	Percentage
1	LUNG	20	51.28%
2	THYROID	4	10.26%
3	GIT(colon)	2	5.13%
4	FGT	2	5.13%
5	BREAST	1	2.56%
6	UNKNOWNPRIMARY/ DETAILS UNAVAILABLE	10	25.64%
7	TOTAL CASES	39	100%

In this study among the 39 cases of metastatic deposits, males (24 cases) were most commonly affected than females (15 cases). Among the 20 cases of lung carcinoma, 15 cases (38.47%) were males and 5 cases (12.82%) are females. This is shown in (Table 11 and Chart 11).

TABLE – 11

SEX WISE DISTRIBUTION OF PRIMARY TUMOURS PRODUCED DEPOSITS IN NERVOUS SYSTEM

S.no	Primary tumour	Male (no)	%	Female(no)	%
1	LUNG	15	38.47%	5	12.82%
2	THYROID	1	2.56%	3	7.69%
3	GIT	2	5.13%	0	0
4	FGT	0	0	2	5.13%
5	BREAST	0	0	1	2.56%
6	UNKNOWN/PRIMARY DETAILS UNAVAILABLE	6	15.38%	4	10.26%
7	TOTAL CASES	24	61.54%	15	38.46%

WHO GRADE I tumour constituted 11 cases (47.83%). WHO a GRADE III tumour constituted 13.04%.Grading of primary papillary tumours was shown in this table. (Table 12 and Chart 12)

TABLE – 12

WHO GRADE WISE DISTRIBUTION OF PRIMARY NERVOUS SYSTEM TUMOURS WITH PAPILLARY PATTERN

S.no	WHO GRADE	Number of cases	Percentage
1	WHO GRADE I	11	47.83%
2	WHO GRADE II	3	13.04%
3	WHO GRADE III	7	30.43%
4	WHO GRADE IV	2	8.70%
5	TOTAL CASES	23	100%

We used a panel of IHC markers for 56 cases. Blocks were not available for 2 cases of papillary meningioma, one case of choroid plexus carcinoma, one case of papillary ependymoma, one case of choroid plexus carcinoma with focal atypia and one case of PNET. GFAP showed positivity in 6 cases (10.70%) of Myxopapillary ependymoma, 1 case of papillary meningioma and one case of ependymoblastoma. All 39 cases (69.64%) of secondary metastatic deposits showed GFAP negativity. (Table 13)

TABLE – 13

GFAP EXPRESSION IN NERVOUS SYSTEM TUMOURS WITH PAPILLARY PATTERN

S.no	Histomorphology	GFAP+VE (NO)	%	GFAP-VE(NO)	%
1	Myxopapillary ependymoma	6	10.70%	1	1.79%
2	Papillary meningioma	1	1.79%	2	3.57%
3	Choroid plexus papilloma	0	0	2	3.57%
4	Choroid plexus papilloma with focal atypia	0	0	1	1.79%
5	Choroid plexus carcinoma	0	0	1	1.79%
6	Papillary variant of craniopharyngioma	0	0	2	3.57%
7	Ependymoblastoma	1	1.79%	0	0
8	Metastatic papillary adeno carcinomatous deposits	0	0	39	69.64%
9	Total	9	14.28%	47	85.72%

This study showed pan cytokeratin positivity in 39 cases (69.64%) of metastatic deposits, 2 cases (3.57%) of choroid plexus papilloma and one case of choroid plexus papilloma with focal atypia. (Table 14)

TABLE – 14

CYTOKERATIN EXPRESSION IN NERVOUS SYSTEM TUMOURS WITH PAPILLARY PATTERN

S.no	Histomorphology	CK+VE (NO)	%	CK-VE(NO)	%
1	Myxopapillary ependymoma	0	0	7	12.5%
2	Papillary meningioma	0	0	3	5.36%
3	Choroid plexus papilloma	2	3.57%	0	0
4	Choroid plexus papilloma with focal atypia	1	1.79	0	0
5	Choroid plexus carcinoma	0	0	1	1.79%
6	Papillary variant of craniopharyngioma	0	0	2	3.57%
7	Ependymoblastoma	0	0	1	1.79%
8	Metastatic papillary adeno carcinomatous deposits	39	69.64%	0	0
9	Total	42	75%	14	25%

S-100 protein studied showed positivity in 2(3.57%) cases of choroid plexus papilloma and one case of choroid plexus papilloma with focal atypia. All other tumours were negative for S-100 protein. (Table 15).

TABLE – 15

S-100 PROTEIN EXPRESSION IN NERVOUS SYSTEM TUMOURS WITH PAPILLARY PATTERN

S. no	Histomorphology	S-100+VE (NO)	%	S-100-VE(NO)	%
1	Myxopapillary ependymoma	0	0	7	12.5%
2	Papillary meningioma	0	0	3	5.36%
3	Choroid plexus papilloma	2	3.57%	0	0
4	Choroid plexus papilloma with focal atypia	1	1.79	0	0
5	Choroid plexus carcinoma	0	0	1	1.79%
6	Papillary variant of craniopharyngioma	0	0	2	3.57%
7	Ependymoblastoma	1	1.79%	0	0
8	Metastatic papillary adeno carcinomatous deposits	0	0	39	69.64%
9	Total	3	5.36	53	94.64%

Vimentin studied in this study shows positivity in 3 cases of papillary meningioma and one case of myxopapillary ependymoma. All other tumours were negative for vimentin with in the tumour cells. (Table 16).

TABLE – 16

VIMENTIN EXPRESSION IN PAPILLARY NEOPLASMS OF NERVOUS SYSTEM

S. no	Histomorphology	VIM +Ve (NO)	%	VIM- Ve (NO)	%
1	Myxopapillary ependymoma	1	1.79%	6	10.70%
2	Papillary meningioma	3	5.36%	0	0
3	Choroid plexus papilloma	0	0	2	3.57%
4	Choroid plexus papilloma with focal atypia	0	0	1	1.79%
5	Choroid plexus carcinoma	0	0	1	1.79%
6	Papillary variant of craniopharyngioma	0	0	2	3.57%
7	Ependymoblastoma	1	1.79%	0	0
8	Metastatic papillary adeno carcinomatous deposits	0	0	39	69.64%
9	Total	4	7.15%	52	92.85%

Carcino embryonic antigen showed positivity in all 39 cases of (69.64%) metastatic deposits. None of the primary tumours showed positivity. (Table 17).

TABLE – 17

CARCINO EMBRYONIC ANTIGEN IN PAPILLARY NEOPLASMS OF NERVOUS SYSTEM

S. no	Histomorphology	CEA+Ve (NO)	%	CEA-Ve (NO)	%
1	Myxopapillary ependymoma	0	0	7	12.5%
2	Papillary meningioma	0	0	3	5.36%
3	Choroid plexus papilloma	0	0	2	3.57%
4	Choroid plexus papilloma with focal atypia	0	0	1	1.79%
5	Choroid plexus carcinoma	0	0	1	1.79%
6	Papillary variant of craniopharyngioma	0	0	2	3.57%
7	Ependymoblastoma	0	0	1	1.79%
8	Metastatic papillary adeno carcinomatous deposits	39	69.64%	0	0
9	Total	39	69.64%	17	30.36 %

Epithelial membrane antigen studied showed positivity in 37 cases (66.07%) of metastatic deposits and one case of papillary meningioma. (Table 18).

TABLE – 18

EPITHELIAL MEMBRANE ANTIGEN EXPRESSION IN PAPILLARY NEOPLASMS OF NERVOUS SYSTEM

S. no	Histomorphology	EMA+ Ve (NO)	%	EMA- Ve (NO)	%
1	Myxopapillary ependymoma	0	0	7	12.5%
2	Papillary meningioma	1	1.79%	2	3.57%
3	Choroid plexus papilloma	0	0	2	3.57%
4	Choroid plexus papilloma with focal atypia	0	0	1	1.79%
5	Choroid plexus carcinoma	0	0	1	1.79%
6	Papillary variant of craniopharyngioma	0	0	2	3.57%
7	Ependymoblastoma	0	0	1	1.79%
8	Metastatic papillary adeno carcinomatous deposits	37	66.07%	2	3.57%
9	Total	38	67.86%	18	32.14%

In this study 4 cases of thyroid carcinoma metastasis showed thyroglobulin, CEA and CK positivity. Because of economic constraints other panels of antibodies to find out unknown primary was not used in this study.

DISCUSSION

Nervous system tumours are increasing in incidence in both developed and developing countries in the present era. Both adults and paediatric population show increasing occurrence of nervous system tumours.

*** EPIDEMIOLOGY OF NERVOUS SYSTEM TUMOURs IN GENERAL:**

* In the present study, histomorphological and immunohistochemical evaluation was done in 56 cases of papillary neoplasms and an attempt to differentiate each papillary neoplasm has been made with the use of a panel of IHC markers.

* Madras Medical College being a tertiary referral centre, the relative percentage of nervous system tumours among neuropathology samples was 79.48%. 20.22% were non neoplastic lesions. Among the nervous system tumours 62 cases were papillary neoplasms which constituted about 2.66%.

* In this study Male: Female ratio of nervous system tumours was 2:1.

* As per WHO statistics nervous system tumours account for about 1.9% of overall tumour incidence in males and 1.8% in females[57]. In paediatric age group, nervous system tumours are one of the most common solid tumours. As per Gurney et al[58], CNS tumours are the

second most commonly distributed (20.7%) tumours after leukemia (23.2%).

* In India as per ICMR[59] statistics, annual percentage change in brain cancer for males in Chennai was 3.0%, for females in Chennai was 4.6%.
* ICMR and WHO statistics are population based studies. This study is a tertiary care hospital based descriptive study.
* This study showed that secondary metastatic carcinomatous deposits with papillary architecture constituted the most common nervous system tumours with an incidence of 62.90%. This is in concurrence with WHO statistics[60], KE Smedby et al, Barnholtz-Sloan et al. [11,12]

*** DESCRIPTIVE STUDY OF PAPILLARY NEOPLAMS OF NERVOUS SYSTEM:**

*** PRIMARY PAPILLARY NEOPLASMS:**

*** Choroid plexus tumours:**

* Among 62 cases of papillary neoplasms, primary papillary tumours of nervous system constituted about 23 cases with a relative percentage of about 37%.
* In this study choroid plexus tumour constituted about 6 cases with a relative percentage of about 10%. The peak age was between 1-15 years. Among 6 cases of choroid plexus

tumour, 3 cases occurred in children ≤ 1 year of age with a relative percentage of 5%. This is in concurrent with WHO analysis[61].

* As per WHO[61] among all brain tumours, choroid plexus tumours account for 0.3 – 0.6%; 2 – 4% of those occur in children less than 15 years of age. 10 % of those occur in 1st year of life. This is slightly higher than the present study.

* Among 6 cases of choroid plexus tumours, 2 cases were choroid plexus papillomas (WHO Grade I) , 2 cases were choroid plexus papilloma with atypia (WHO Grade II) and 2 cases were choroid plexus carcinoma (WHO Grade III) with relative percentage of about 3%.

* As per Janish et al, Rickert et al and Wolff et al[18, 19, 62] 80% of Choroid plexus carcinoma arise in children in whom they constitute 20 – 40% of chroid plexus tumours. In the present study choroid plexus carcinoma constituted about 33%. This is in concurrence with the study of Janish et al[18]

* In this study among 6 cases, 4 cases presented as a lateral ventricle mass with a relative percentage of 67% among choroid plexus tumours. This is in concurrence with

WHO[61] analysis. 2 cases presented as a third ventricle SOL (33%).

* The overall male: female ratio was 1:1. This ratio was 1:1 for lateral ventricle tumours and 3rd ventricle tumours. This is similar to the WHO[61] study.

* Myxopapillary ependymoma:
  * Myxopapillary ependymoma constituted the most common intra medullary neoplasm in this study. Among 7cases, 6 were intra medullary, predominantly involving lumbar region. This is in concurrent with Kurt et al and Schiffer et al[63,64]
  * Age range was 17 – 60 years with a male predominance. The male: female ratio was 6:1. This is in concurrent with Cervoni et al [17] study in which average age of presentation was 36 years with an age range of 6 to 82 years and Male: female ratio was about 2.2:1
  * In this study the most common site was lumbar region. As per WHO almost they exclusively occur in conus medullaris and filum terminale

* Papillary meningioma:
    * Ludwin et al,[49] described the clinico pathologic features of 17 cases and found that in comparison to other variants of meningiomas, PM was more frequent in children; 8/17(47%). Mitoses were seen in 7/17(41%), local recurrences in 10/ 17(59%), brain invasion in 8/17(47%), and extra cranial metastasis in 4/17(23.5%). This was not in concurrence with the present study
    * Radhakrishnan et al.,[65] reported 6 cases of PM all of which occurred in adults and most of them showed histological evidence of bone and brain invasion. This is in concurrence with the present study.
    * In the present study 5 cases were reported as papillary meningioma with a relative percentage of about 8%. All cases occurred in male patients with an age range of 18 to 53 years. This is in concurrence with the study of Radhakrishnan et al[65]. Among 5 cases, 2 cases were papillary meningioma with rhabdoid differentiation. For 2 cases paraffin blocks were not available.

* Papillary craniopharyngioma:
    * Among 62 papillary tumours, 2 cases were papillary craniopharyngioma. As per Adamson et al and Crotty et al[23,24] papillary craniopharyngioma occurs exclusively in adults with a median age range of 40 – 55 years. In the present study age range was 20 – 40 years. Compare to Crotty et al[24] the age group was younger in this study. Male: female ratio was 1:1. Sellar location was common in both studies.
* Papillary ependymoma:
    * One case of papillary ependymoma was reported in 18 years male in lateral ventricle. Block was not available for histological and IHC analysis.
* Metastatic papillary tumours of nervous system:
    * Metastatic papillary tumour included 39 cases with a relative percentage of 63 %. This is in concurrence with Barnholtz et al and K E Smedby et al[11, 12].
    * Among 39 cases, 24 cases were males with a relative percentage of 39%. 15 cases were female patients with a percentage of 24%. This is in concurrence with Barnholtz et al and Ksmedby et al[11, 12].

* Most common histological pattern was papillary adeno carcinomatous deposits. Among 39 cases, 28 cases were known primary. 23 cases with lung as primary constituted 37% of papillary neoplasms; 59% of secondary adenocarcinomatous deposit; 1 case was thyroid carcinoma, 2 cases were from GIT, 2 cases from ovarian malignancy. This is in concurrence with K E Smedby et al, Jill et al and WHO[11,12,60].

* Most common affected age group was between 41-60 years with a male predominance of about 24 cases with percentage of 39%; among metastasis percentage of males was 62%. This is in concurrence with WHO, & Jill et al [60,11]. Females constituted 15 cases with an overall percentage of 24%, among metastasis 38%.

* In this study, anatomical site wise analysis revealed that cerebrum was the most commonly affected region in the nervous system. Among 39 cases, 29 (47%) occurred in cerebrum, 7(11%) cases were in posterior fossa, 3(5%) cases were in spinal cord. This study is similar to WHO analysis[60].

* Among the cerebral lobes, frontal lobe was the most commonly affected lobe by metastasis. 13 cases occurred in frontal lobe followed by 7 cases in temperoparietal, and 5 cases parieto occipital. This was in concurrence with WHO analysis and Jill et al[60,11].

*** HISTO MORPHOLOGY OF PAPILLARY TUMOUS:**

*** Primary papillary tumours:**

* Among 6 cases of choroid plexus tumour, 2 were WHO grade I choroid plexus papilloma, 2 cases were WHO grade II choroid plexus papilloma with atypia, 2 cases were WHO grade III choroid plexus carcinoma. CPP showed papillary pattern with central delicate fibro vascular core. These cores are lined by uniform single layer of cuboidal to columnar cells. Cells have oval to round, basally situated uniform nuclei. They have very low mitotic activity. Atypical choroid plexus papilloma showed increase mitotic activity. This is similar to WHO analysis [61]
* CPC showed patternless diffuse sheets with ill defined papillary pattern. They showed >5 mitosis per 10HPF with increased nuclear pleomorphism.

* All 7 myxopapillary ependymomas were WHO grade I tumour. They showed arrangement of cells in a papillary pattern around blood vessels. The cells were cuboidal to columnar with myxoid material in the background. This is similar to WHO analysis[66].
* Among 5 cases of papillay meningioma blocks were available for 3 cases only. These were WHO grade III tumours. They showed ill defined papillary pattern and diffuse pattern with adjacent brain parenchymal infiltration. In this 2 cases showed rhabdoid differentiation. Rhabdoid cells are plump oval cells with eccentrically placed nuclei with open chromatin and prominent nucleoli. Cytoplasm is waxy eosinophilic in nature.
* 2 cases of papillary craniopharyngioma were reported. These are WHO grade I tumours. They showed well differentiated squamous epithelium in papillary pattern.

*** Metastatic papillary tumours:**

***** Among 39 cases, 36 cases showed well defined papillary pattern of cells with central fibrovascular core. The cells lining the papillae were columnar cells showing stratification with increased N: C ratio and coarse hyperchromatic nuclei. Foci of necrosis were also seen.

* 2 cases of lung primary showed vague papillae and bronchiole alveolar pattern of cells. The cells are arranged in papillary pattern with oedematous fibro vascular core. The lining cells are low columnar with peg like appearance.
* 2 cases of primary thyroid carcinoma showed papillary and follicular arrangement of cells. The cells are round to oval with clear nuclei with nuclear crowding and overlapping. The follicle contains colloid.

* **IMMUNO HISTOCHEMISTRY IN NERVOUS SYSTEM TUMOURS:**

* **Primary papillary tumours:**

* In the present study we used a panel of immunohistochemical markers including Glial Fibrillary Acidic Protein, Pan Cytokeratin, Epithelial Membrane Antigen, S-100, Vimentin and carcino embryonic antigen. Blocks were not available for 2 cases of papillary meningioma, one case of choroid plexus carcinoma, one case of papillary ependymoma, one case of choroid plexus carcinoma with focal atypia and one case of PNET.
* IHC staining was graded similar to Doglioni et al[(67)] by using semi quantitative scale ranging from -(no

immunoreactive cells) to 4+ (75-100% of the neoplastic cells are immunostained) The symbols 1+, 2+, and 3+ refer to the immunostaining of up to 25%, 25-50%, and 50-75% of the neoplastic cells, respectively.

* In this study out of 4 cases of choroid plexus tumours, 3 cases showed strong (4+) Cytokeratin positivity. These 3 cases were CPP & ACPP. This is concurrence with Ang et al, Doglioni et al and Mannoji et al [53,67,54] study.CPC showed negativity for CK. This is differing from Ang et al[53] study.(Table 17,18,19)

* In Ang et al[53] study choroid plexus tumour showed focal GFAP positivity. This is in contradiction to the present study which showed GFAP negativity in all 6 cases of choroid plexus tumour. (Table 17,18,19)

* CPP and ACPP showed strong S-100 (3+) positivity. This is in concurrence with Ang et al study and Doglioni et al[53,67]. (Table 17,18,19)

* Vessel wall in the fibro vascular core showed strong Vimentin (4+) positivity.

* In concurrence with Ang et al[53] study, all choroid plexus tumours showed complete negativity for CEA.(Table 17,18,19)
* None of the choroid plexus carcinoma showed S-100, Vimentin, EMA and CEA positivity.

TABLE – 17

IHC EXPRESSION IN CHOROID PLEXUS PAPILLOMA IN DIFFERENT STUDIES

Choroid plexus papilloma(IHC)	Ang et al[53]	Doglioni et al[67]	Mannoji et al[54]	Current study
GFAP	2(5)-Focal	6(13)	6(11)	0(2)
CK	5(5)	8(13)	11(11)	2(2)
S-100	4(5)	13(13)	-	2(2)
VIM	1(5)	11(13)	-	0(2)
CEA	0(5)	-	-	0(2)
EMA	-	8(13)	-	0(2)

TABLE – 18

IHC EXPRESSION IN CHOROID PLEXUS PAPILLOMA WITH FOCAL ATYPIA IN DIFFERENT STUDIES

Choroid plexus papilloma with focal atypia (IHC)	Ang et al[53]	Current study
GFAP	1(1)- Focal	0(1)
CK	1(1)	1(1)
S-100	1(1)	1(02)
VIM	0(1)	0(1)
CEA	0(1)	0(1)
EMA	-	0(1)

TABLE – 19

IHC EXPRESSION IN CHOROID PLEXUS CARCINOMA IN DIFFERENT STUDIES

Choroid plexus carcinoma(IHC)	Doglioni et al[67]	Mannoji et al[54]	Current study
GFAP	2(3)	1(4)	0(1)
CK	3(3)	4(4)	0(1)
S-100	2(3)	-	0(1)
VIM	3(3)	-	0(1)
CEA	-	-	0(1)
EMA	3(3)	-	0(1)

All 6 cases of myxopapillary ependymoma showed GFAP 4+ positivity in neuroepithelial cells and Vimentin 4+ positivity in blood vessels. This is in concurrence with Ang et al and Doglioni et al[53, 67]. One case showed Vimentin positivity in tumour cells with GFAP

negativity. All 7 cases were non reactive for CK, S-100 and CEA. This is in concurrence with Ang et al and Doglioni et al[53,67] study.

TABLE – 20

IHC EXPRESSION IN MYXOPAPILLARY EPENDYMOMA IN DIFFERENT STUDIES

Myxopapillary ependymoma(IHC)	Ang et al[53]	Mannoji et al[54]	Current study
GFAP	2(2)	2(2)	6(7)
CK	0(2)	0(2)	0(7)
S-100	0(2)	-	0(7)
VIM	2(2)	-	1(7)
CEA	0(2)	-	0(7)
EMA	-	-	0(7)

In this study IHC was done on 3 cases of papillary meningioma. One case was done in private hospital. Details of IHC were obtained from records. It showed strong 4+ for Vimentin and GFAP positivity was seen only in non neoplastic brain parenchyma. One case showed EMA

positivity. This is concurrent with Avninder et al, Radhakrishnan et al and Ludwin et al[69,65,49].

All cases papillary meningioma were non reactive for CK, EMA and CEA. This is similar to Ang et al study[53].

One case of ependymoblastoma showed GFAP, S-100, Vimentin 4+ positivity, CK 2+ positivity. This is similar to Ehret et al, Cruz et al, Mannoji et al and Parkkila et al study.[70,71,54,72].

All primary papillary tumours were non reactive for CEA. This is similar to Ang et al study[53].

* **Metastatic papillary tumours:**

Among 39 cases of metastatic papillary tumours 36 showed CK 4+ positivity. 2 showed 2+ positivity and one showed (1+) positivity. All 39 cases were non reactive for S-100.This is in concurrence with Ang et al and Gottschalk et al[53,73] study.

Similar to Ang et al[53] study, all metastatic papillary tumours showed CK and CEA 4+ positivity. Thyroid carcinoma showed 4+ positivity for thyroglobulin and CEA. (Table 19)

TABLE – 19

IHC EXPRESSION IN METASTATIC DEPOSITS IN DIFFERENT STUDIES

Metastatic deposits(IHC)	Ang et al[53]	Current study
GFAP	0(7)	0(39)
CK	7(7)	39(39)
S-100	0(7)	0(39)
VIM	0(7)	0(39)
CEA	6(7)	39(39)
EMA	-	37(39)

CEA is an useful marker to differentiate between primary and secondary tumours. This antibody is useful to differentiate the papillary neoplasms.

*** IHC SUMMARY:**

All myxopapillary ependymomas expressed both GFAP and VM, which were absent in all choroid plexus tumours. In contrast, all choroid plexus tumours showed anti-cytokeratin immunoreactivity that was

absent in the all myxo papillary ependymomas. 3 choroid plexus tumours also expressed S-100 P, thus differentiating them from metastatic carcinoma that showed negative immunostaining. Anti-CEA antisera immunoreactivity was seen in 39 tumours, whereas none of the primary CNS tumours expressed CEA. This is concurrent with Ang et al study[53].

STRENGTH AND LIMITATIONS OF THIS STUDY:

* STRENGTH OF THIS STUDY:

1. Study covers a period of 5 years done at a tertiary care hospital in south India.
2. A papillary pattern seen in various CNS tumours. These have been studied extensively both histomorphologically and immunohistochemically in correlation with clinical parameters.
3. A wide panel of markers have been studied which include
    a. Markers for primary papillary tumours
    b. Markers for differentiating primary and secondary papillary tumours
    c. Organ specific markers used for specific cases

* LIMITATIONS OF THIS STUDY:

1. Study is hospital based, hence does not reflect the true incidence and prevalence in the community.
2. Due to economic constraints, the entire panel of antibodies for each case could not be used.
3. Follow up was not available and not analysed.

SUMMARY

- A total of 2932 neuro surgical samples received at a tertiary care centre have been analysed. Of these the non neoplastic lesions constituted 20.23%, and neoplastic lesions of nervous system were 79.57%.

- In a study period of 5 years, 62 cases of nervous system tumours with papillary pattern were subjected to histological and Immunohistochemical analysis to find out the usefulness of IHC in their diagnosis and differential diagnosis. The findings were correlated with WHO grading and analysis.

- The relative frequency of nervous system tumours with papillary pattern among other nervous system tumours in Madras Medical College was 2.66%

- Metastatic tumours with papillary pattern constituted 62.90% and this formed the most common tumours of nervous system. The peak age group was between 51 to 60 years with relative percentage of 20.97%.

- Males were most commonly affected in both primary and secondary papillary tumour with an overall percentage of 27.42% in primary tumours, 38.71% in secondary tumours.

- Primary lung carcinoma was the most common cause of nervous system metastasis in both males and females which constituted 20 cases and relative percentage of 51.28% among metastatic tumours.

- Unknown primary/details not available cases constituted about 10 cases with percentage of 25.64%.

- In primary nervous system tumours with papillary pattern most common age group was between 0 to 10 years with a relative percentage 11.29%.

- In the 0-10 years age group, the most common tumours with papillary pattern were Choroid plexus tumour which constituted about 6 cases with relative overall incidence of 9.68% and 26.09% among primary tumours.

- Most common site for primary papillary tumour was spinal cord which constituted 9 cases (14.52%) with a relative percentage of 39.12% among primary papillary tumours.

- Myxopapillary ependymoma was the most common spinal cord papillary tumour which constituted about 7 cases with relative percentage of 30.43% among primary tumours.

- Within the cerebral hemisphere ventricles were the most common site for primary papillary tumours which is 6 cases with relative percentage of 26.09%.

- In metastatic papillary tumours cerebrum was the most common site with a relative percentage of 74.36% among secondary deposits.

- In cerebrum, frontal lobe was the most common site for secondary deposits with papillary pattern which constituted 13 cases with relative percentage of 44.83%.

- WHO GRADE I tumours were the most common primary tumours which constituted 11 cases with relative percentage of 47.83%.

- On Immunohistochemistry analysis GFAP expression was commonly seen in Myxopapillary ependymoma which included 6 cases with 10.70% relative incidence.

- Pan cytokeratin positivity was seen in all 39 (69.64%) cases of metastatic deposits and both cases 2 cases (3.57%) of choroid plexus papilloma.

- S-100 protein studied showed positivity in both 2(3.57%) cases of choroid plexus papilloma.

- Vimentin studied in this study showed positivity in all 3(5.36%) cases of papillary meningioma and one case of myxopapillary ependymoma. All other tumours were negative for vimentin within the tumour cells.

- Carcino embryonic antigen showed positivity in all 39 cases of (69.64%) metastatic deposits. None of the primary tumours showed positivity.

- Epithelial membrane antigen studied showed positivity in 37 cases (66.07%) of metastatic deposits and one case of papillary meningioma.

CONCLUSION

- The incidence of papillary neoplasms of nervous system in this study was 2.66%.

- Metastatic deposits with papillary pattern constituted a higher percentage and older age group has higher incidence similar to western population.

- Lung carcinoma producing brain metastasis constituted higher incidence similar to western population.

- In younger age group most of the papillary tumours were choroid plexus tumours.

- Most of the papillary meningiomas were seen in young adults. All patients were adult males.

- Immunohistochemistry used in this study was useful to differentiate primary from secondary tumours and to diagnose primary papillary tumours.

- Carcino embryonic antigen is an important marker to differentiate primary from secondary papillary tumours.

- We need more immunohistochemistry panels to know the primary site for secondary papillary tumours.

- Use of these IHC markers aids us to know about individual tumour antigen expression, to diagnose difficult cases and for the correct management by clinicians.

❖ **RECOMMENDATIONS :**

- Taking into the consideration the paucity of data on CNS tumours, it is recommended to maintain a "**Comprehensive CNS Tumour Registry"** at the tertiary care hospital level.

- This would help in generation of valuable input for proper planning and management.

- Data from the registry will also help to get clear epidemiological picture of CNS tumours in Indian settings.

- Further studies can be directed at adding further specific IHC markers and the role of proliferation indices to this study.

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ANNEXURE I

PROFORMA

Case no :

OP/IP NO :

Name :

Biopsy No :

Age :

Sex :

Clinical diagnosis :

Symptoms :

H/O Recurrence :

Risk factors any :

CT/MRI findings :

Site :

Contrast enhancement :

Side :

Ventricle obstruction :

Solid :

Cystic with mural nodule :

Cystic:

Type of surgery :

Gross :

Size:

Papillary excrescence:

Necrosis:

Microscopy :

Histological typing:

WHO grading:

Grade I Grade III

Grade II Grade IV

IHC RESULTS :(Positivity & Semi quantitative Score 1-4+)

GFAP :

CK :

EMA :

S-100 :

Vimentin :

CEA :

ER :

PR :

Thyroglobulin :

ANNEXURE II

WHO GRADING OF NERVOUS SYSTEM TUMOURS

GRADE I : Neoplasms with low proliferative tendency

GRADE II : Neoplasms with cytological atypia alone

GRADE III : Neoplasms with anaplasia and mitotic activity

GRADE IV : Neoplasms with micro vascular proliferation and/or necrosis

S.NO	Biopsy NO	Age	Sex	Complaints	CT/MRI	Gross	H&E	IHC	GFAP	CK	S-100	Vimentin	CEA	EMA	Thyroglobulin	ER	PR
1	9/07	40 Y	M	Headache	Hyper dense	MGWST	Secondary papillary		-	+++	-	-	+++	+++			
2	69/07	35 Y	M	Headache	Hyper dense	MGWST,C/S-	Carcinoma thyroid		-	+++	-	-	+++	+++	+++		
3	148/07	56 Y	M	Headache	Heterodense	MGWST	Secondary papillary		-	+++	-	-	+++	+++			
4	195/07	57 Y	M	Headache,cerebellar	Mixed contrast	MGWST	Secondary papillary		-	+++	-	-	+++	+++			
5	220/07	60 Y	M	Giddiness, head ache	Left cerebellar	MGWST	Secondary papillary		-	+++	-	-	+++	+++			
6	227/07	55 Y	M	fever, head ache	Hyper dense	MGBST	Secondary papillary		-	+++	-	-	+++	+++			
7	238/07	53 Y	M	head ache	Well defined	MGBST with	Secondary papillary		-	+++	-	-	+++	+++			
8	248/07	65 Y	M	head ache	hyper dense	MGWST	Secondary papillary		-	+++	-	-	+++	+++			
9	281/07	60 Y	M	Upper limb & lower limb	Left tempero	MGBST	Secondary papillary		-	++++	-	-	+++	-			
110	458/07	45 Y	M	seizure, head ache	Ring enhancing	MGWST with	Secondary papillary		Negative	+++	-	-	+++	+++			
11	16/08	45 Y	M	weakness of upper limb &	supra Sellar	MGW& GB ST	Secondary papillary		-	++++	-	-	+++	+++			
12	72/08	50 Y	M	vomiting, head ache	Left occipital	MGWST	Secondary papillary		-	++++	-	-	+++	+++			

13	308/08	47 Y	M	weakness of upper limb &	well defined	MGBST	Secondary papillary		-	+++	-	-	+++	+++		
14	529/08	23 Y	M	seizure, head ache	Left temporal	MGWST with	Secondary carcinomatou		-	+++	-	-	+++	+++		
15	373/08	42 Y	M	head ache, vomiting	Left Parieto	MGBST	Secondary papillary		-	+++	-	-	+++	+++		
16	552/08	65 Y	M	head ache, vomiting,	Right Parieto	MGWST &	Secondary papillary		-	++++	-	-	+++	+++		
17	421/08	54 Y	M	Low back ache	Compression	MGBST & bony	Secondary papillary		-	+++	-	-	+++	+++		
18	122/09	47 Y	M	head ache, seizure	Left parietal	MGWST with	Secondary papillary		-	+++	-	-	+++	+++		
19	556/09	60 Y	M	head ache, vomiting	left tempero	MGBST with	Secondary papillary		-	++++	-	-	+++	-		
20	440/10	52 Y	M	slurring of speech, head	Left tempero	MGBST	Secondary papillary		Negative	+++	-	-	+++	+++		
21	42/11	53 Y	M	head ache, vomiting	circumscribed large	MGBST	Secondary papillary		-	++++	-	-	+++	+++		
22	83/11	45 Y	M	seizure, head ache	Right frontal	MGBST &	Secondary papillary		-	++	-	-	+++	+++		
23	131/11	40 Y	M	head ache, vomiting,	Large left fronto	MGBST	Secondary papillary		-	++	-	-	+++	+++		
24	192/11	45 Y	M	head ache, vomiting	Contrast enhancing	MGBST	Secondary papillary		-	+++	-	-	+++	+++		
25	212/07	30 Y	F	head ache, weakness	Multiple mixed	MGWST	Secondary papillary		-	++++	-	-	+++	+++		
26	304/07	40 Y	F	Low back ache	altered spinal	MGBST & bony	Carcinoma thyroid		-	++++	-	-	+++	+++	+++	

27	371/07	65 Y	F	head ache	Hypo dense	MGBST	Secondary papillary		-	++++	-	-	+++	++			
28	99/08	34 Y	F	Altered sensorium,	multiple hyper	MGBST with	Secondary papillary		-	++++	-	-	+++	++			
29	136/08	55 Y	F	Head ache, giddiness	Right cerebellar	MGWST	Secondary papillary		-	++++	-	-	+++	++			
30	513/08	35 Y	F	head ache	Extra axial	MGBST	Secondary papillary		-	++++	-	-	+++	++			
31	26/09	60 Y	F	head ache, vomiting	Left Parieto	MGWST &	Papillary carcinoma		-	++++	-	-	+++	++	++++		
32	30/09	45 Y	F	sudden weakness	Right parietal	MGBST	Secondary papillary		-	+++	-	-	+++	++			
33	166/09	65 Y	F	seizure, head ache	Multiple hypo	MGBST	Secondary papillary		-	+++	-	-	+++	++			
34	28/10	51 Y	F	Altered sensorium,	Left o fronto	MGWST	Secondary papillary		-	+++	-	-	+++	++			
35	48/10	67 Y	F	head ache, vomiting	Right parietal	MGBST	Secondary papillary		-	+++	-	-	+++	++			
36	411/10	27 Y	F	Giddiness, head ache	Right cerebellar	MGWST	Carcinoma thyroid		-	++++	-	-	+++	++	+++		
37	505/10	50 Y	F	head ache, vomiting	Right frontal	MGBST	Secondary papillary		-	+++	-	-	+++				
38	487/11	50 Y	F	head ache, vomiting	Right frontal	MGWST	Secondary papillary		-	+++	-	-	+++	++		-	-
39	492/11	62 Y	F	Giddiness, head ache	cerebellar SOL	MGBST	Secondary papillary		-	+++	-	-	+++	++			
40	125/07	22 Y	M	Low back ache	L1 intra medullary	GWST	Myxo papillary		+++	-	-	-	-	-			

41	287/07	60 Y	M	Upper limb & lower limb	Intra dural extra	MGWST	Myxo papillary		+++	-	-	-	-	-			
42	82/09	30 Y	M	Right pain thigh	L4-L5 intra dural	MGWST	Myxo papillary		++	-	-	-	-	-			
43	140/09	18 Y	M	Numbness in both limb	D12-L1 intra dural	MGWST	Myxo papillary		+++	-	-	++	-	-			
44	417/11	56 Y	F	Low back ache	Solid & cystic	MGWST	Myxo papillary		+++	-	-	-	-	-			
45	197/08	34 Y	M	weakness of upper limb &	L3-L4 SOL	MGWST	Myxo papillary		+++	-	-	-	-	-			
46	606/11	17 Y	M	Low back ache	L1-L2 intra dural	MGWST	Myxo papillary		-	-	-	-	-	-			
47	14/07	18 Y	M	head ache	Hyper density in	MGWST	papillary meningioma		NA	-	-	NA	-	-			
48	197/07	38 Y	M	head ache, weakness	Right parietal	MGWST	papillary meningioma		+	-	-	+++	-	+++			
49	386/07	21 Y	M	head ache	Hyper dense	MGWST	papillary meningioma		NA	NA	NA	NA	-	NA	NA	NA	NA
50	392/10	27 Y	M	head ache, vomiting	increase in signal	MGWST	papillary meningioma		-	-	-	++	-	-			
51	157/11	53 Y	M	head ache	Right frontal	MGWST	papillary meningioma		-	-	-	+++	-	-			
52	162/07	4/12Y	F	-	Choroid plexus	MGBST	choroid plexus		-	+++	+++	-	-	-			
53	115/09	1Y	F	developmental delay	well circumscri	MGBST	choroid plexus		-	++	++++	-	-	-			
54	479/09	6/12Y	F	Hydrocephalus	Intraventricular	MGBST	choroid plexus		NA	NA	NA	NA	-	-	NA	NA	NA

55	517/11	8Y	M	Hydrocephalus	Posterior 3rd	MGBST	choroid plexus		-	-	+++	++	-	-		
56	460/07	15 Y	M	Hydrocephalus	Right lateral	MGWST	Choroid plexus		NA	NA	NA	NA	-	-	NA	NA	NA
57	363/10	7Y	M	Hydrocephalus	Lateral ventricle	MGBST	Choroid plexus		-	-	-	-	-	-		
58	2/08	36 Y	F	head ache, blurring of	large irregular	MGWST	Papillary variant of		-		-	-	-	-		
59	172/08	20 Y	M	seizure, head ache	Hyper dense	MGWST	Papillary variant of		-		-	-	-	-		
60	335/10	18 Y	M	head ache, blurring of	Sellar SOL with	MGBST and	Papillary ependymoma		NA	NA	NA	NA	-	-	NA	NA	NA
61	163/11	1Y	F	seizure, head ache	Posterior fossa SOL	MWST	Ependymoblastoma		++		++	++	-	-		
62	340/11	1Y	M	weakness of upper limb &	D2-D7 intradural	MWST	PNET		NA	NA	NA	NA	-	-	NA	NA	NA

MASTER CHART KEY WORDS

SOL- space occupying lesion

PNET- primitive neuro ectodermal tumour

MGBST- multiple grey brown soft tissues

MGWST- multiple grey white soft tissues

MWST- multiple whitish soft tissues

+- 1 + positive

++ - 2+ positive

CHARTS

CHART 1: ORIGIN- WISE DISTRIBUTION OF NERVOUS SYSTEM NEOPLASMS WITH PAPILLARY PATTERN

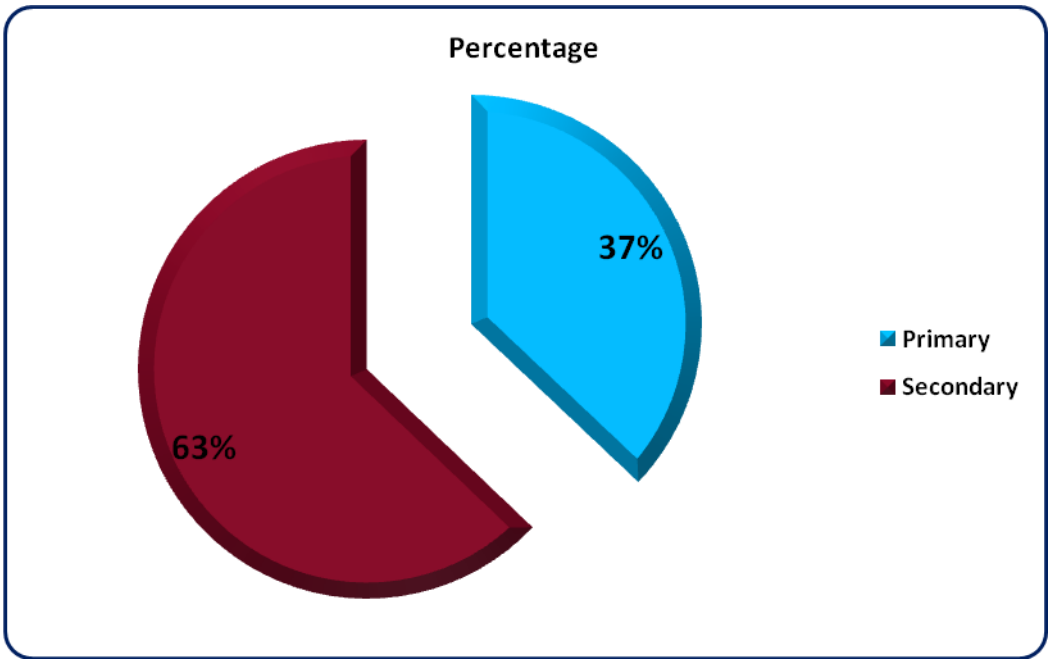


CHART 2: AGE- WISE DISTRIBUTION OF PRIMARY PAPILLARY TUMOURS OF NERVOUS SYSTEM

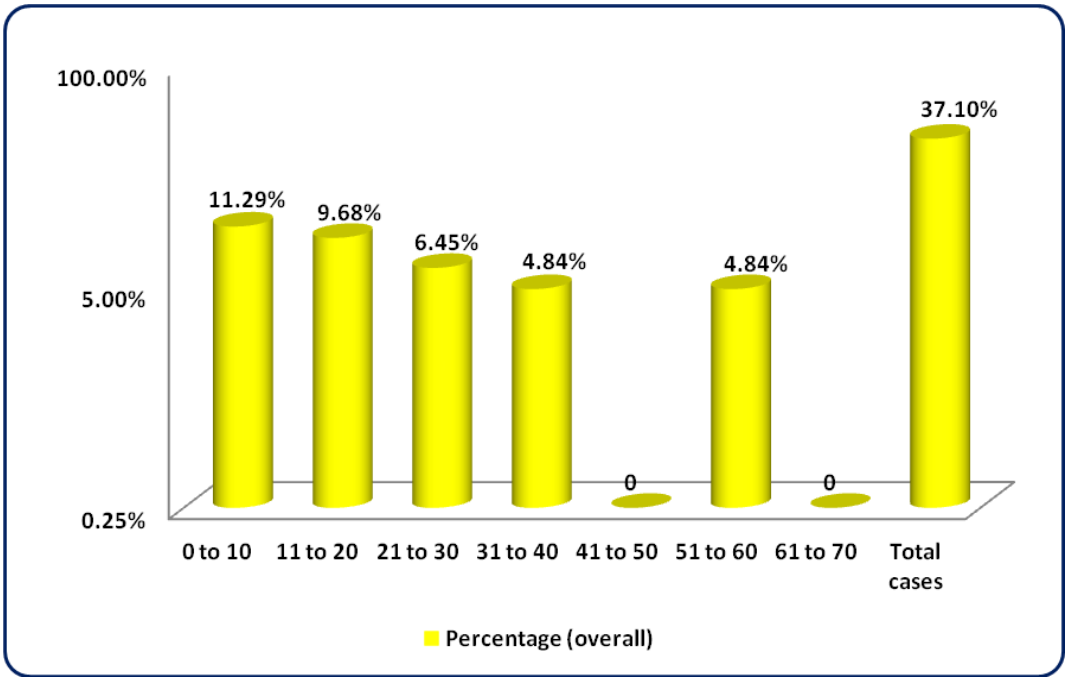


CHART3. AGE --WISE DISTRIBUTION OF METASTATIC PAPILLARY TUMOURS OF NERVOUS SYSTEM

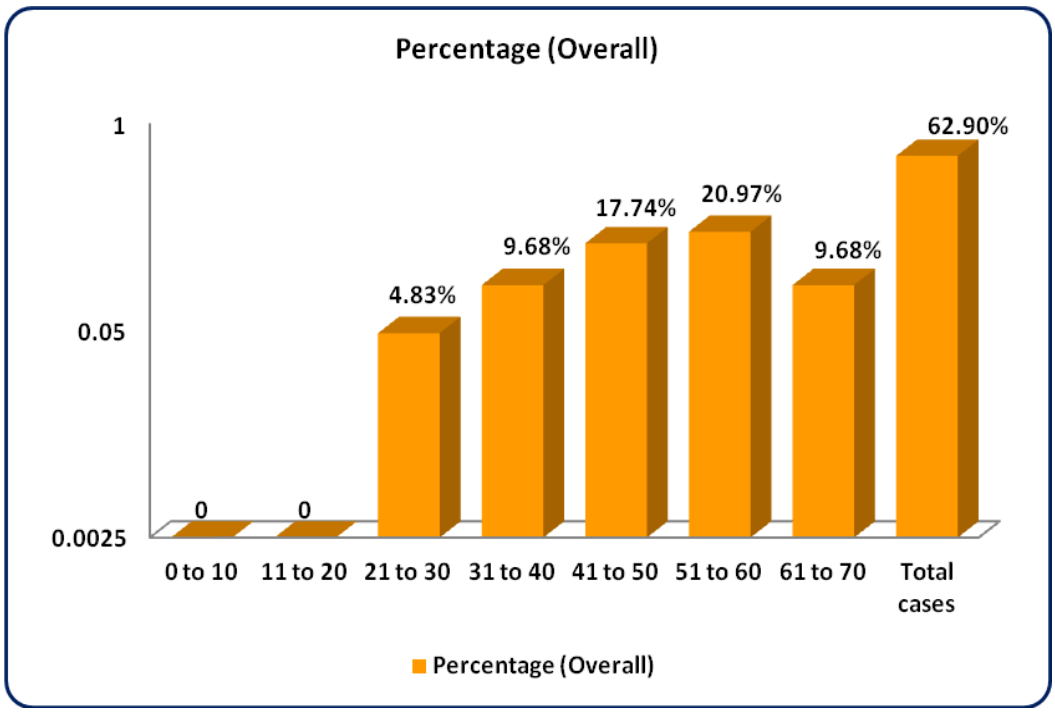


CHART4. SEX- WISE DISTRIBUTION OF PRIMARY PAPILLARY TUMOURS NERVOUS SYSTEM

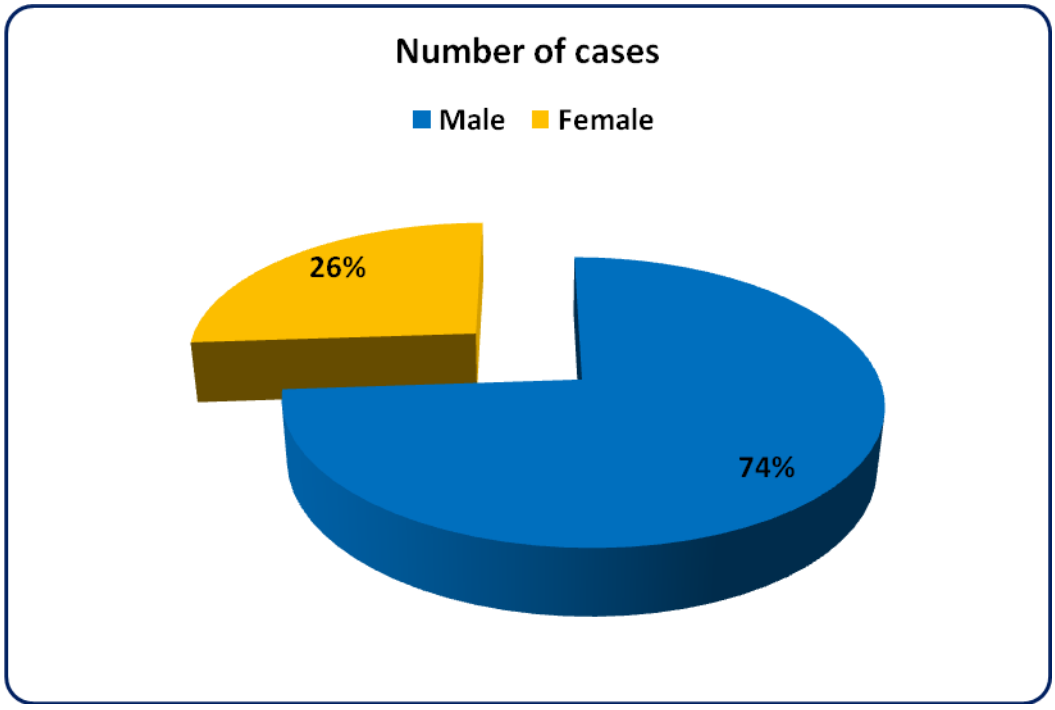


CHART5. SEX- WISE DISTRIBUTION OF METASTATIC PAPILLARY TUMOURS OF NERVOUS SYSTEM

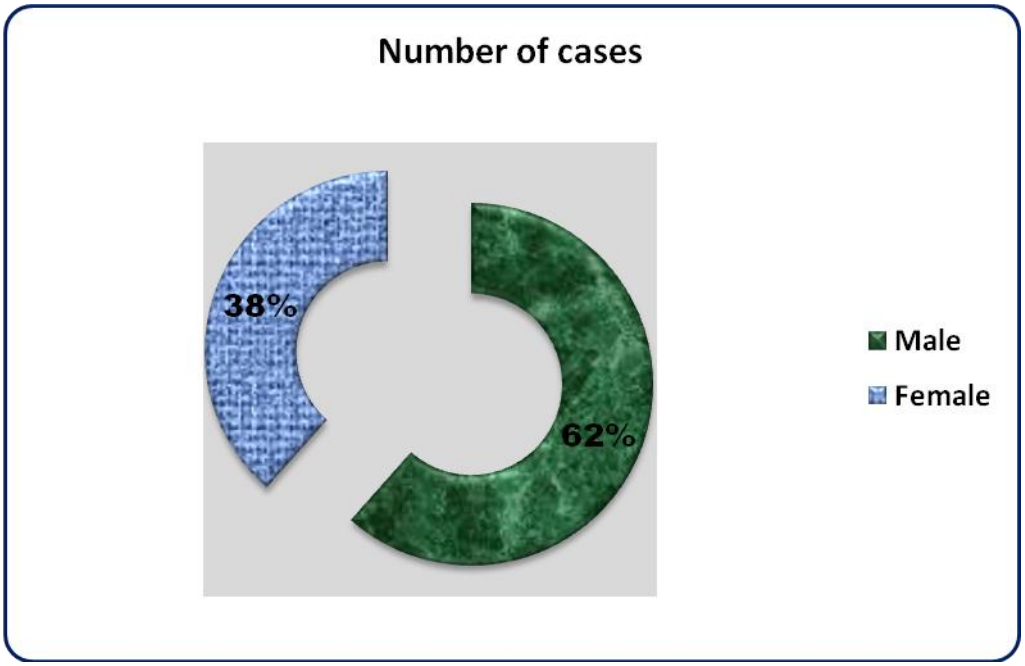


CHART6: SITE -WISE DISTRIBUTION OF PRIMARY PAPILLARY TUMOURS OF NERVOUS SYSTEM

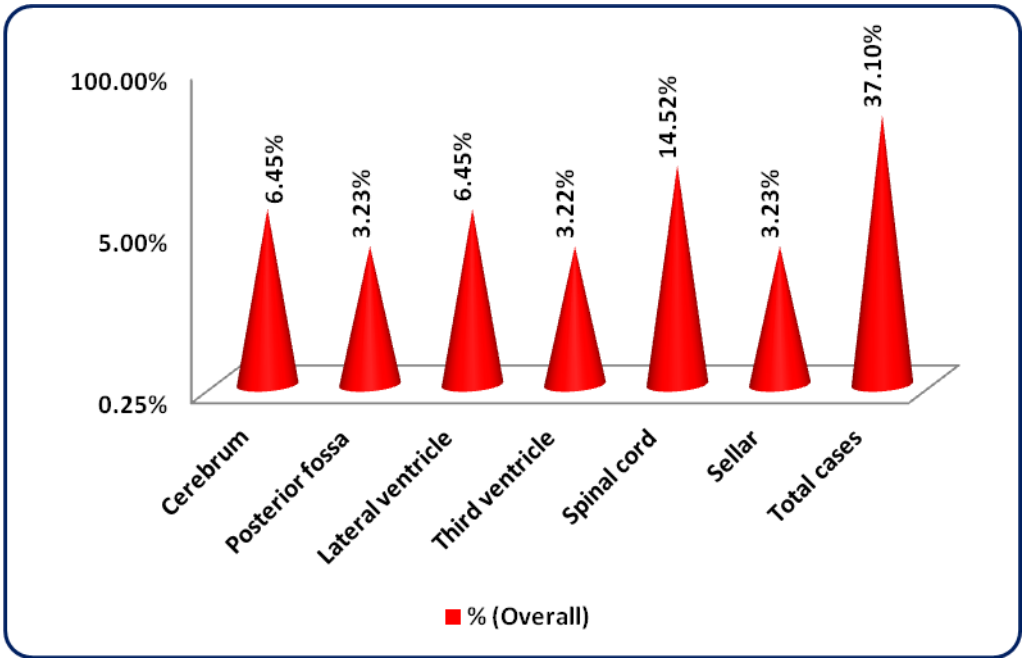


CHART7: SITE -OF DISTRIBUTION OF METASTATIC DEPOSITS IN NERVOUS SYSTEM WITH PAPILLARY PATTERN

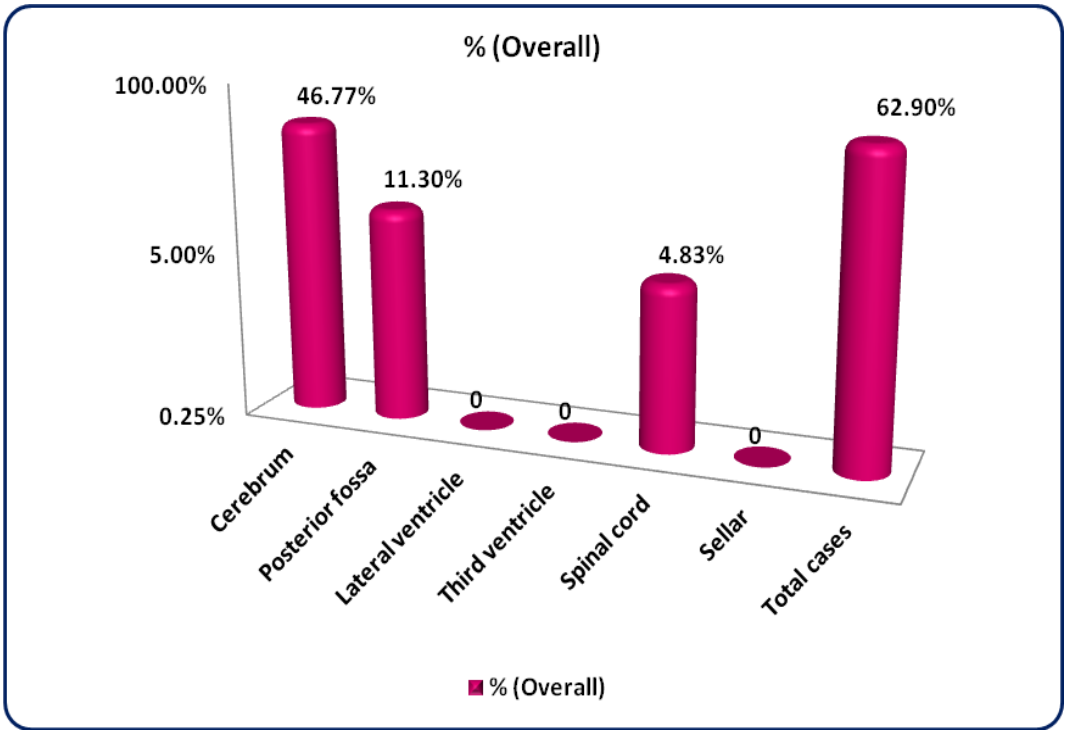


CHART8: CEREBRAL LOBE- WISE DISTRIBUTION OF METASTATIC TUMOUR WITH PAPILLARY PATTERN

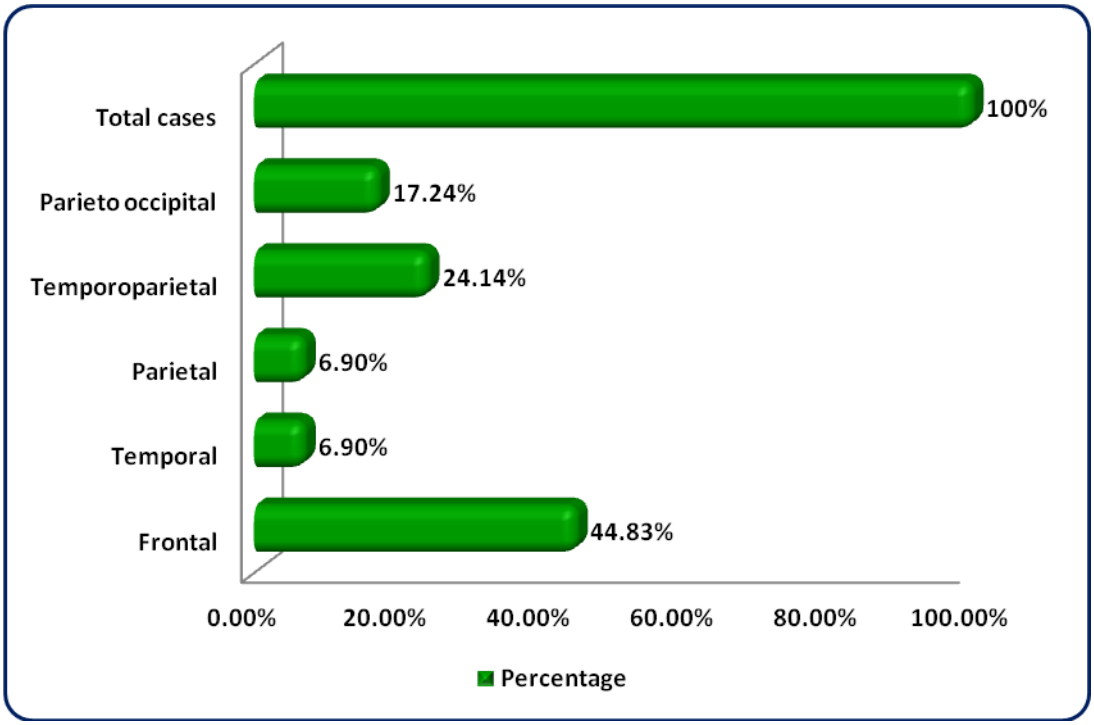


CHART9: HISTOMORPHOLOGICAL DISTRIBUTION OF NERVOUS SYSTEM TUMOURS WITH PAPILLARY PATTERN

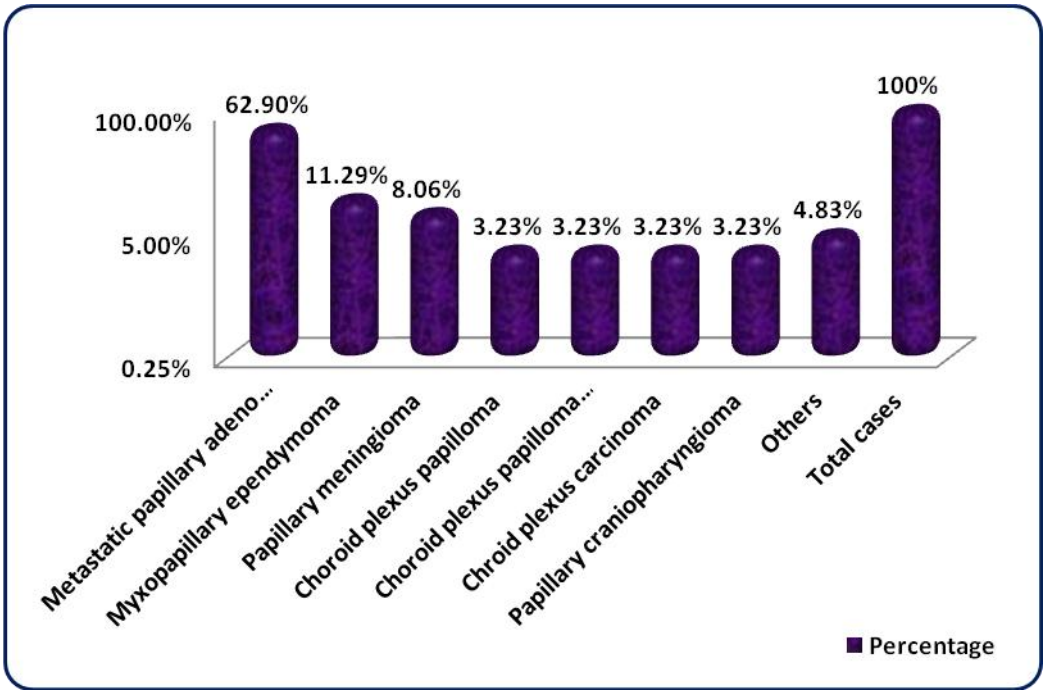


CHART10: PRIMARY TUMOUR WISE DISTRIBUTION OF METASTATIC DEPOSITS WITH PAPILLARY PATTERN

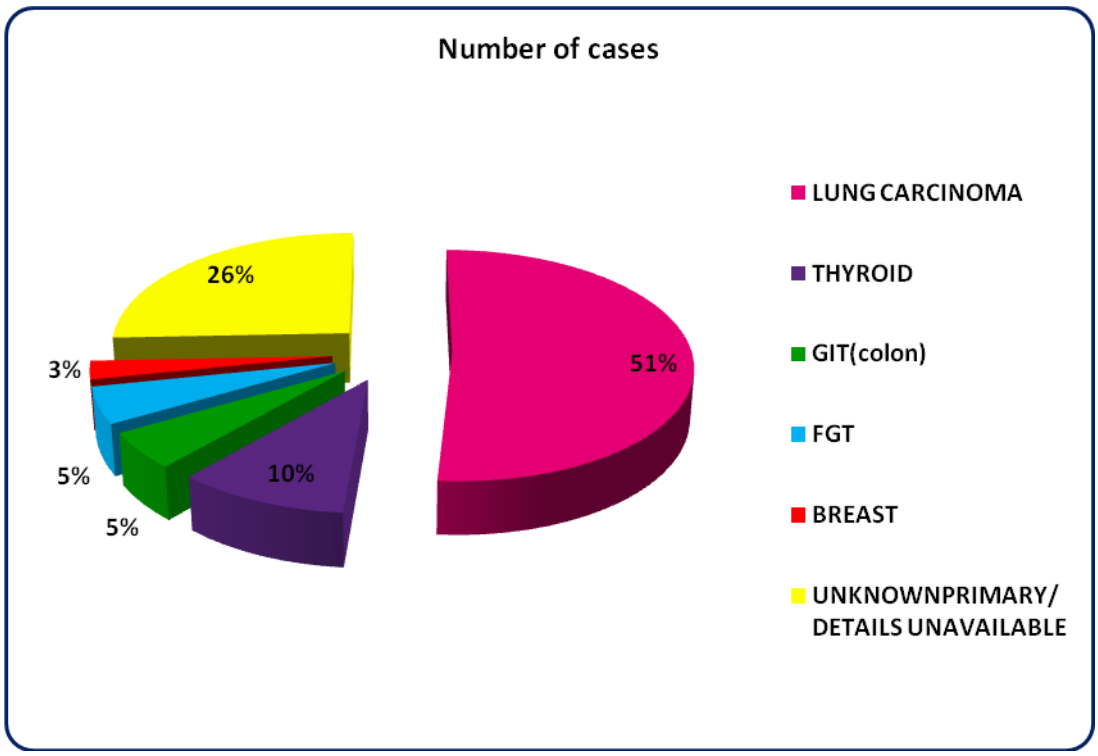


CHART11: SEX WISE DISTRIBUTION OF PRIMARY TUMOURS PRODUCED DEPOSITS IN NERVOUS SYSTEM

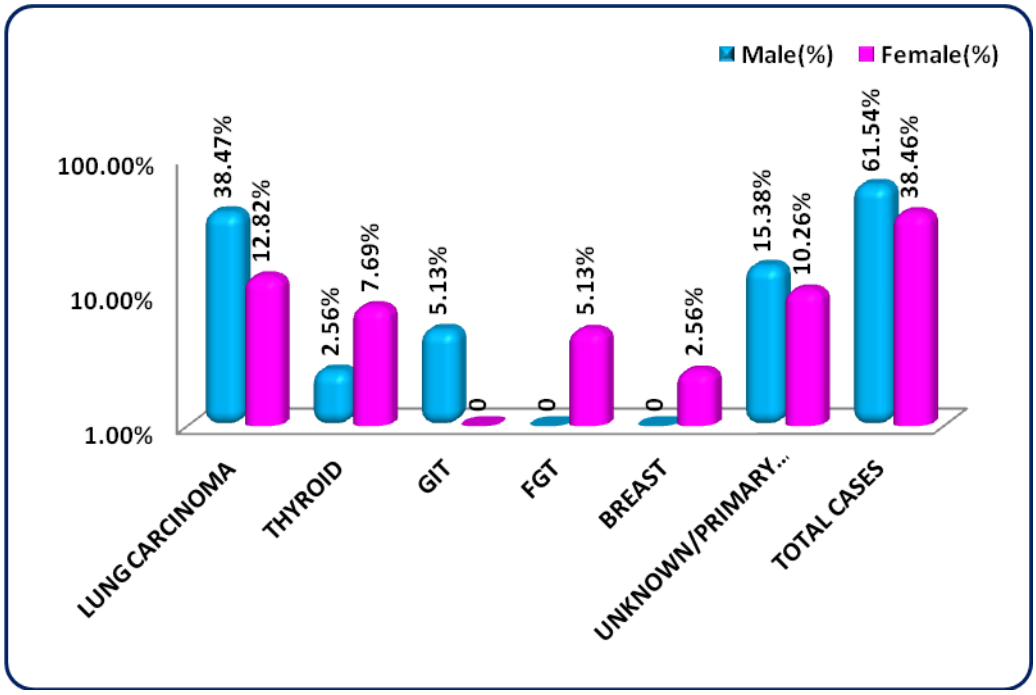
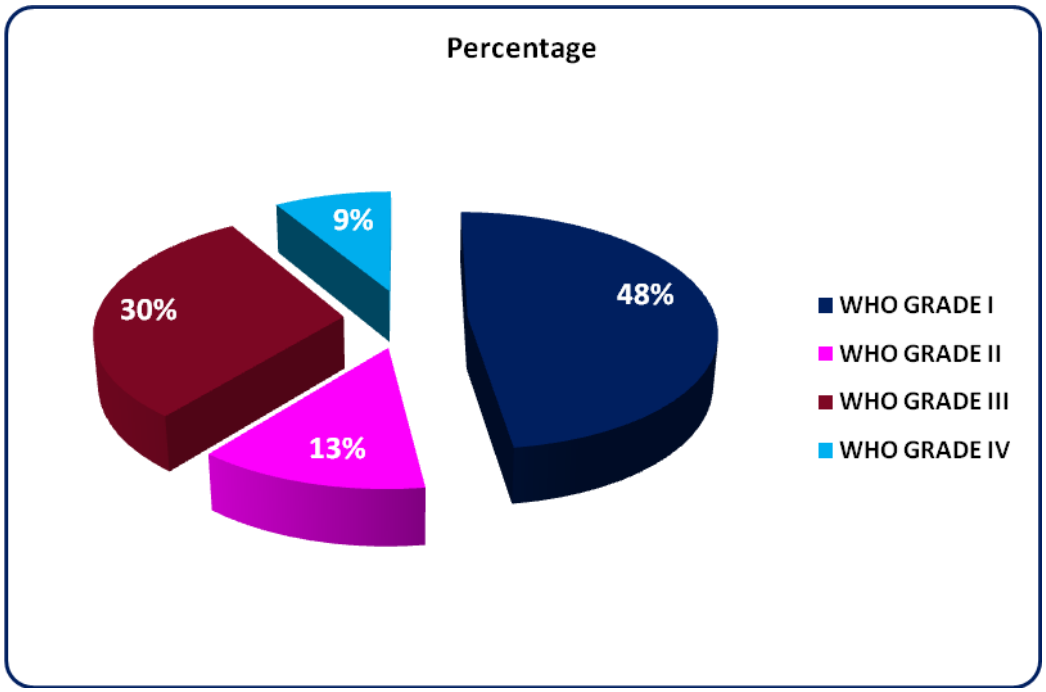


CHART12: WHO GRADE WISE DISTRIBUTION OF PRIMARY NERVOUS SYSTEM TUMOURS WITH PAPILLARY PATTERN



MYXOPAPILLARY EPENDYMOMA

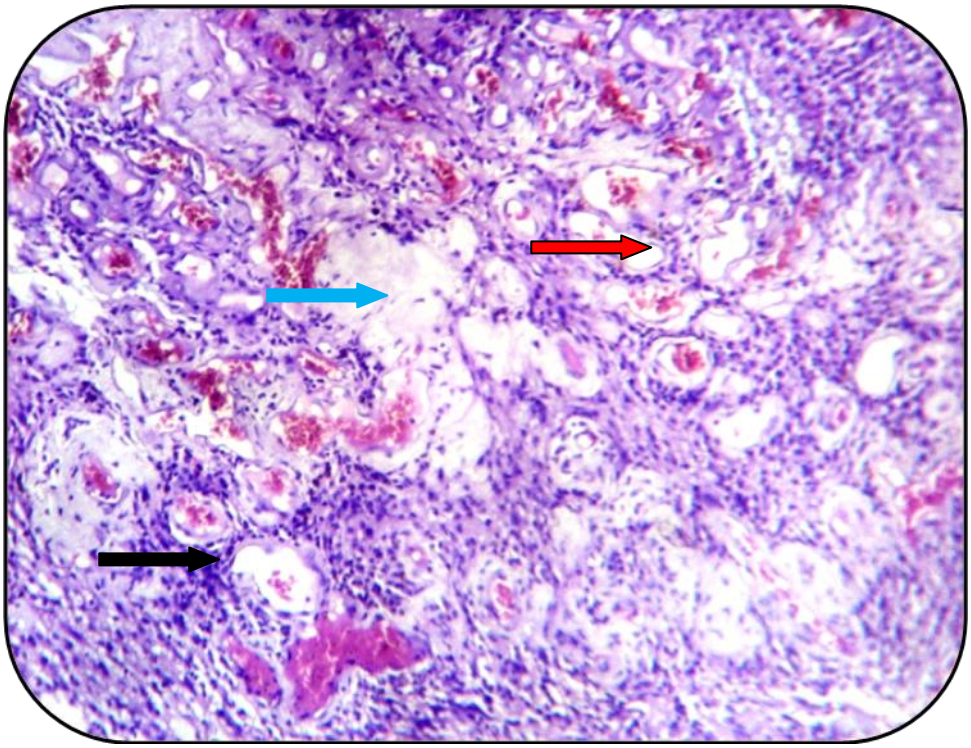


FIG 1: MYXOID (BLUE ARROW) REGION WITH CENTRAL BLOOD VESSEL CORE (RED ARROW) SURROUNDED BY EPENDYMAL CELLS (BLACK ARROW)

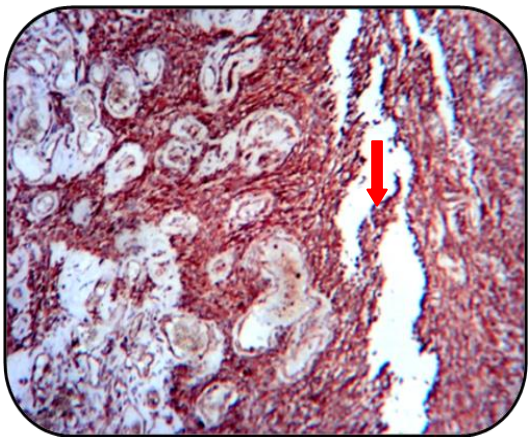


FIG 2: GFAP CYTOPLASMIC POSITIVITY IN EPENDYMAL CELLS

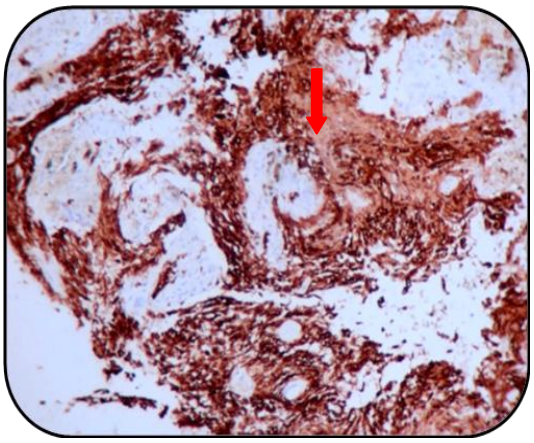


FIG 3: VIM- CYTOPLASMIC POSITIVITY IN EPENDYMAL CELLS

CHOROID PLEXUS PAPILLOMA

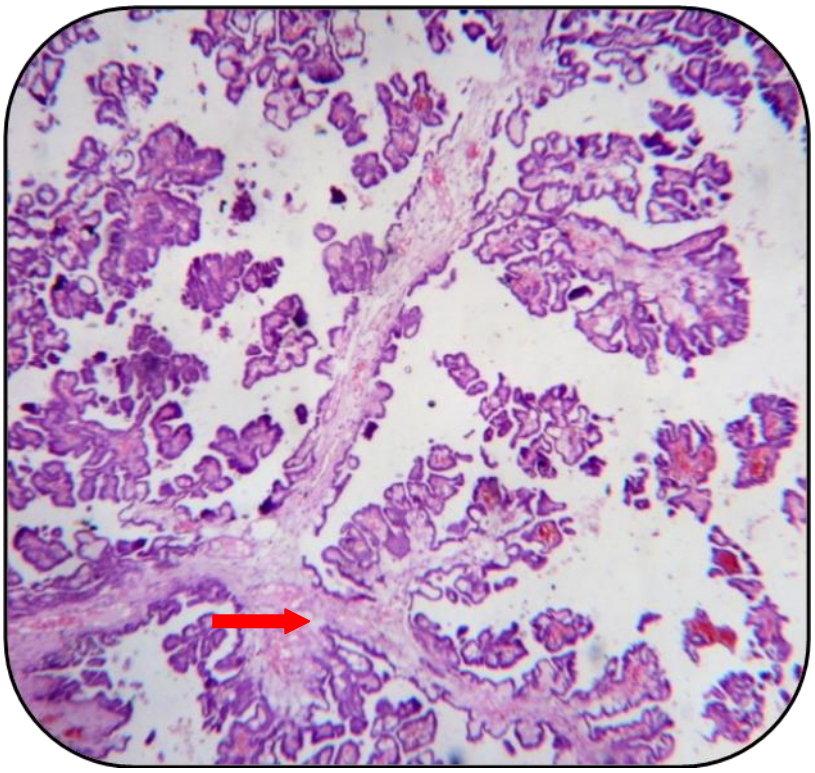


FIG 4: PAPILLARY PATTERN (LOW POWER) (RED ARROW)

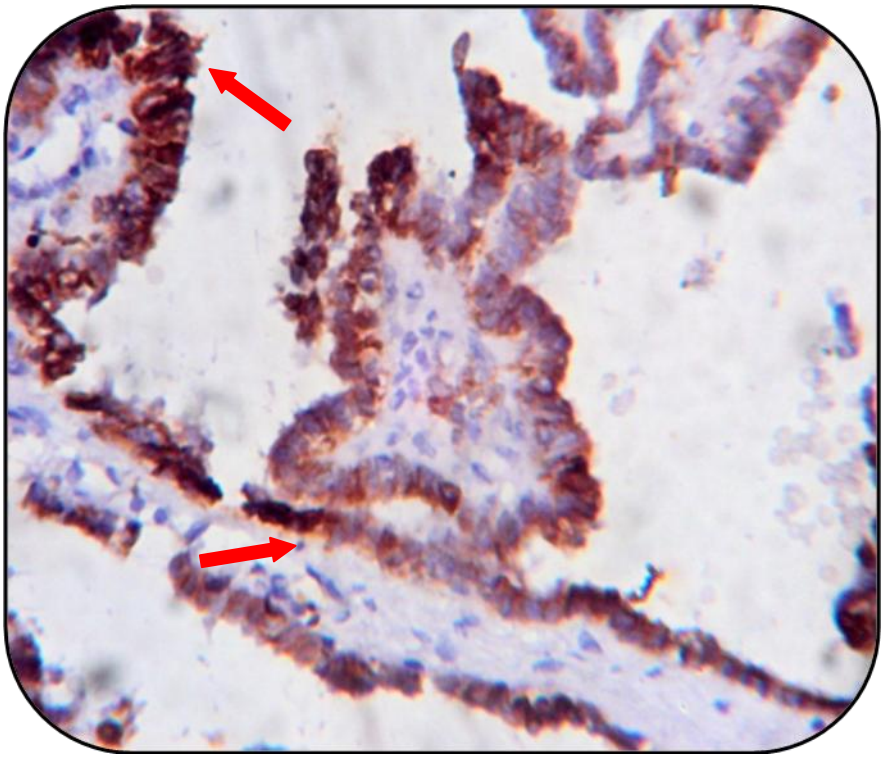


FIG 5: CK- CYTOPLASMIC POSITIVITY IN TUMOUR CELLS (RED ARROW)

CHOROID PLEXUS PAPILLOMA

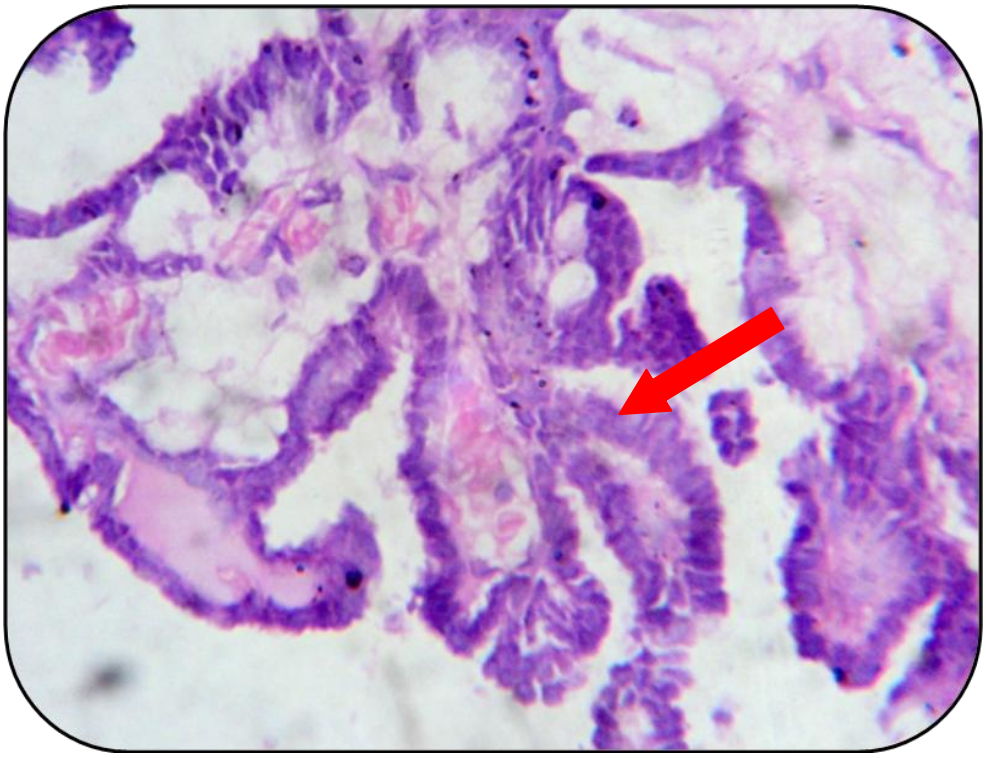


FIG 6: PAPILLARY PATTERN (HIGH POWER- CUBOIDAL TO COLUMNAR CELLS) (RED ARROW)

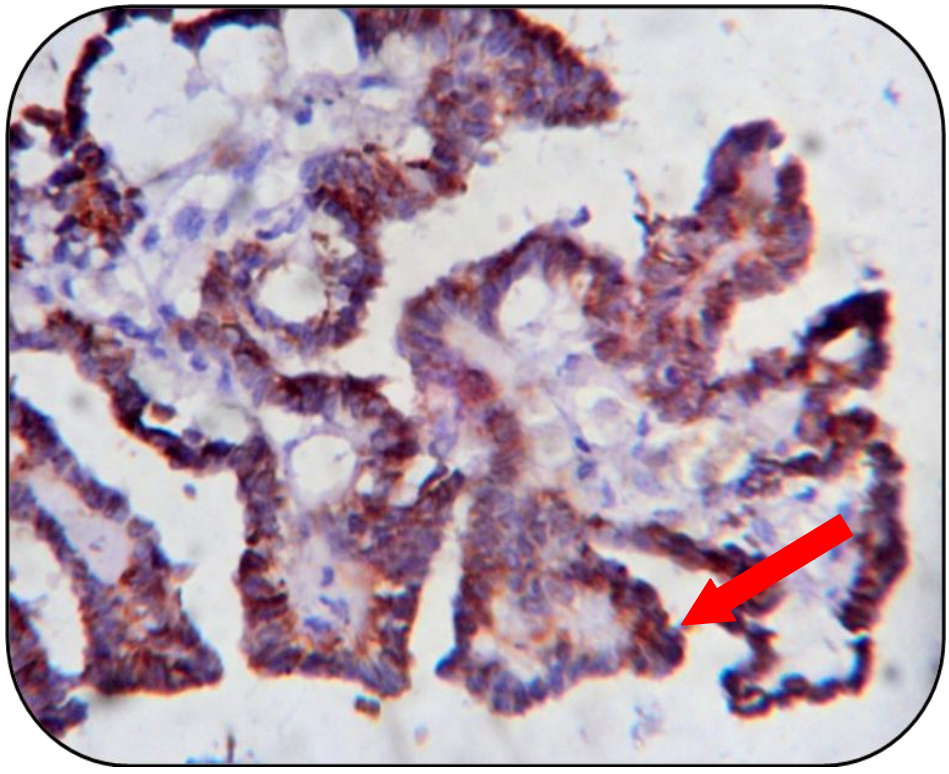


FIG 7: S-100 CYTOPLASMIC POSITIVITY N TUMOUR CELLS

CHOROID PLEXUS PAPILLOMA WITH ATYPIA

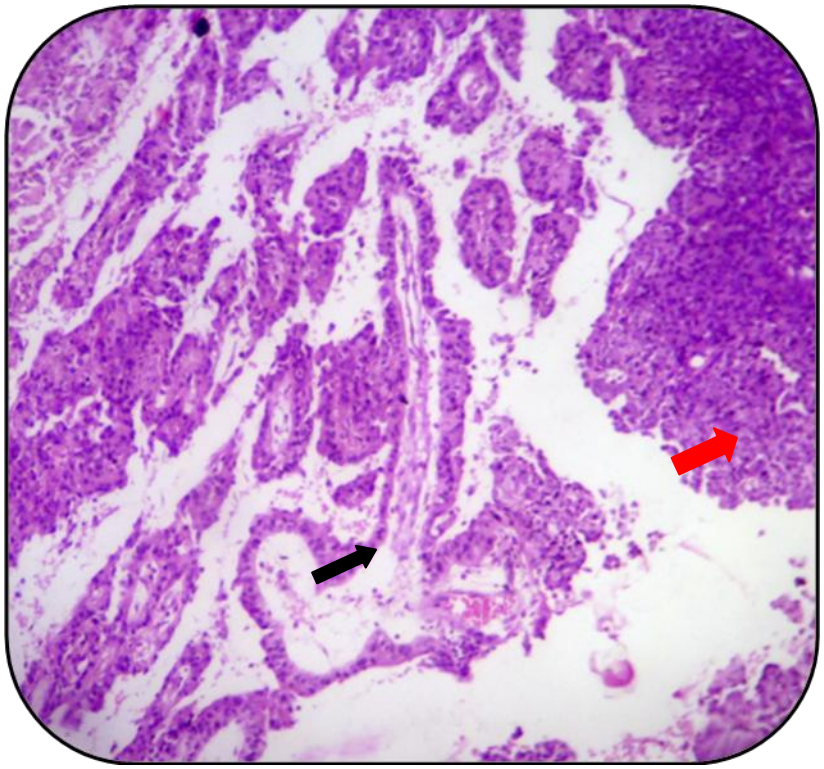


FIG 8: PAPILLARY PATTERN (BLACK ARROW), SOLID SHEET(RED ARROW)

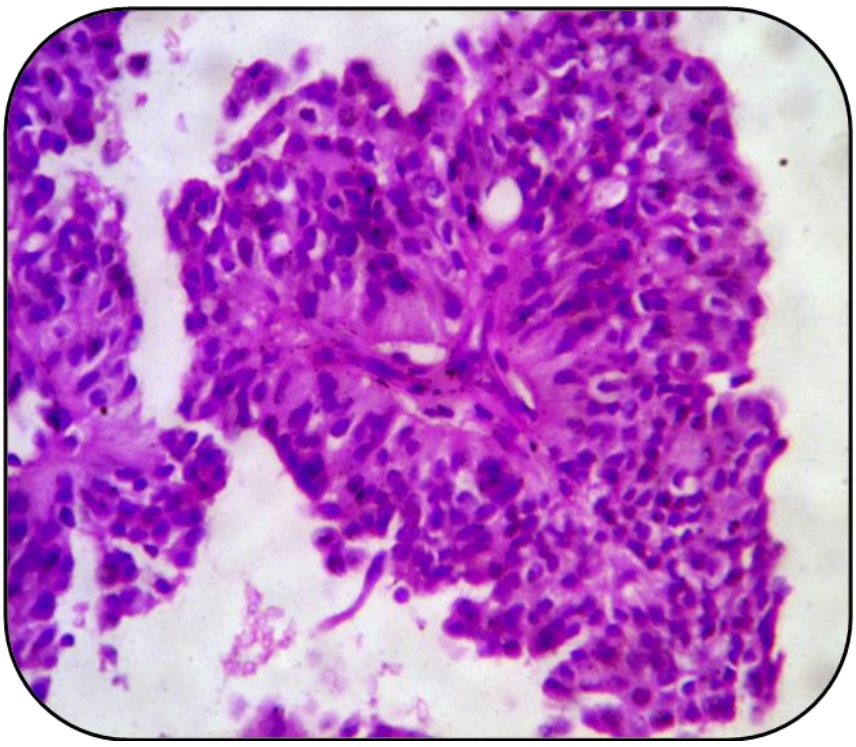


FIG 9: PAPILLARY PATTERN, STRATIFICATION OF CELLS, ATYPIA

CHOROID PLEXUS PAPILLOMA WITH ATYPIA

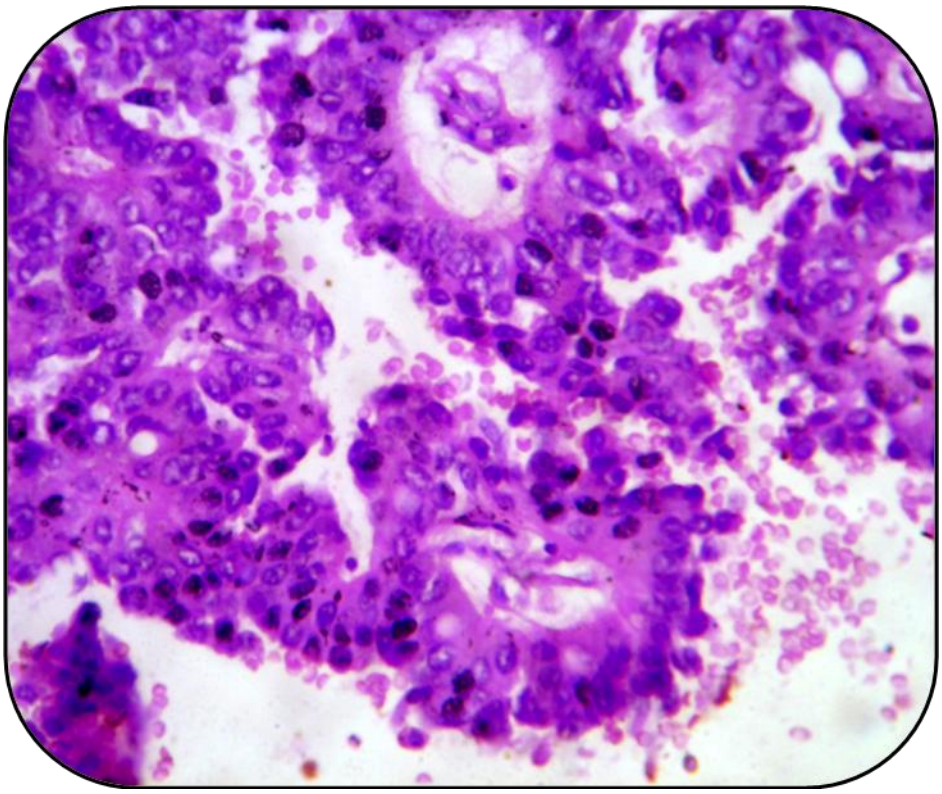


FIG 10: PAPILLARY PATTERN WITH FOCAL ATYPIA

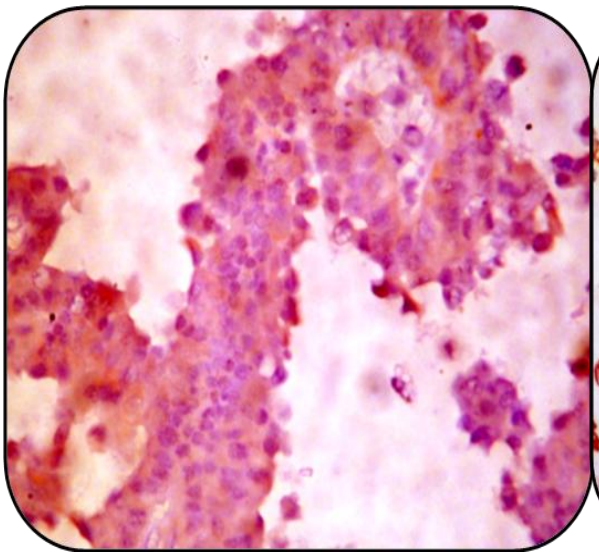


FIG 11: CK- DIFFUSE CYTOPLASMIC POSITIVITY

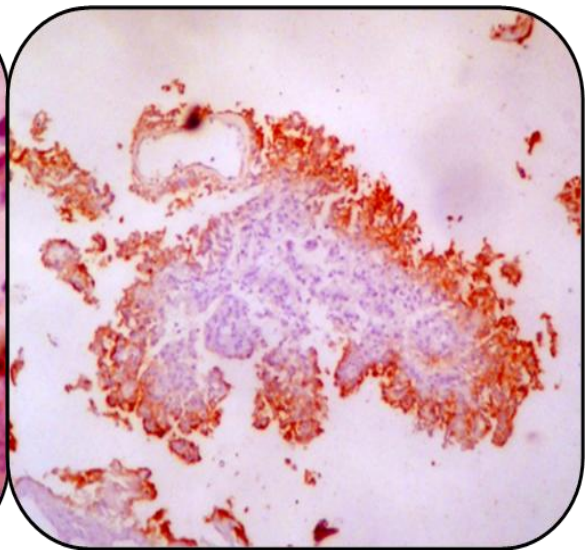


FIG 12: S-100- FOCAL CYTOPLASMIC POSITIVITY

CHOROID PLEXUS CARCINOMA

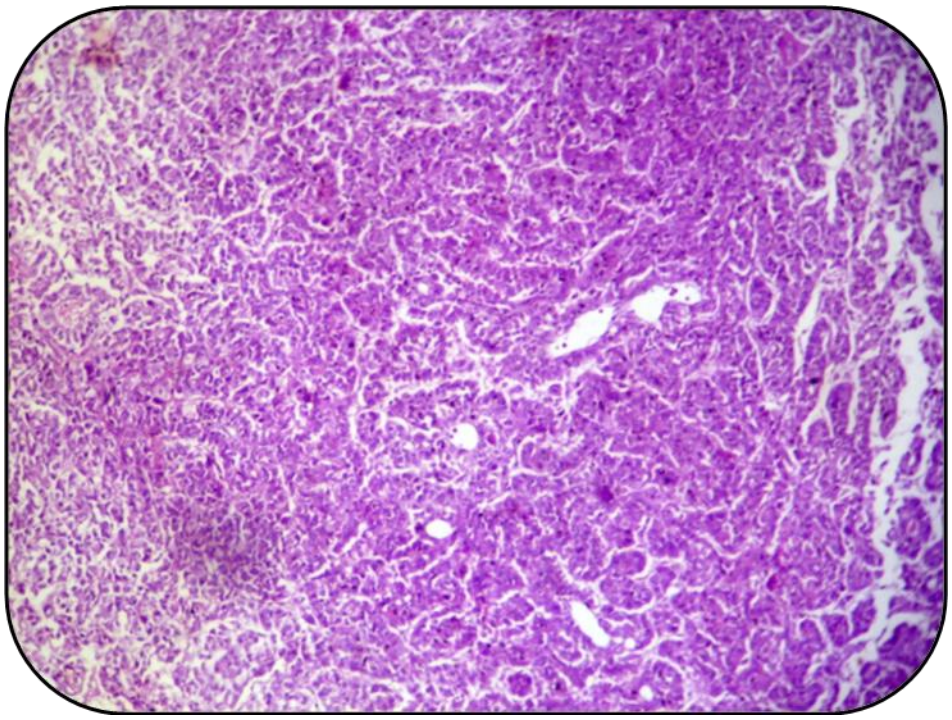


FIG 13: PATTERNLESS SHEETS & FOCAL PAPILLARY PATTERN

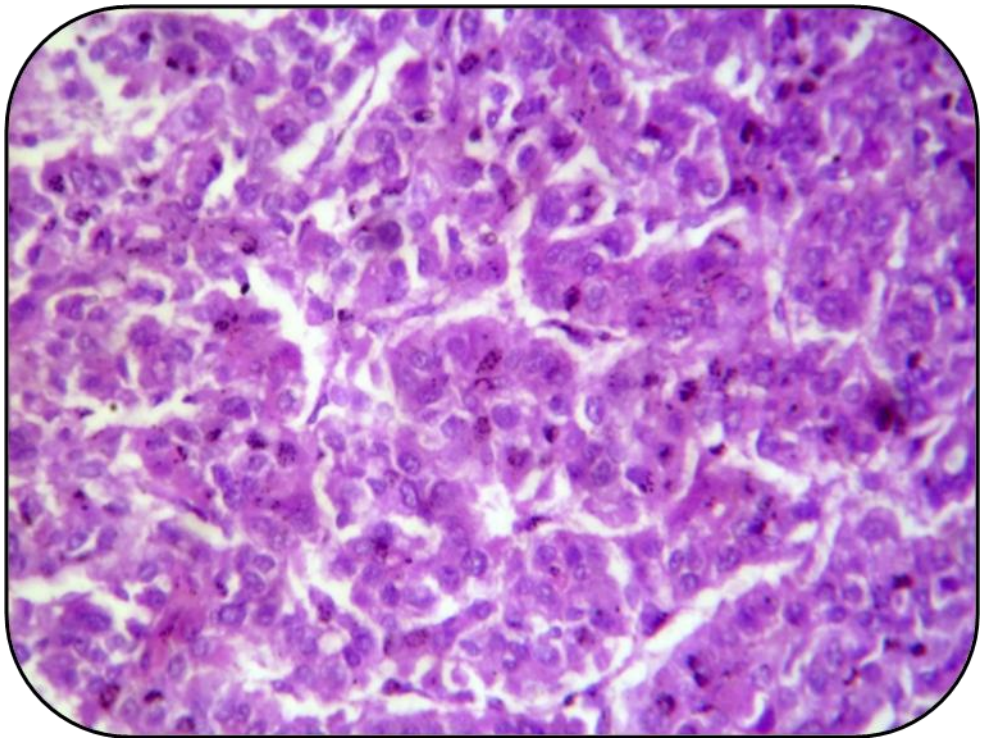


FIG 14: PATTERNLESS SHEETS & FOCAL PAPILLARY PATTERN

CHOROID PLEXUS CARCINOMA

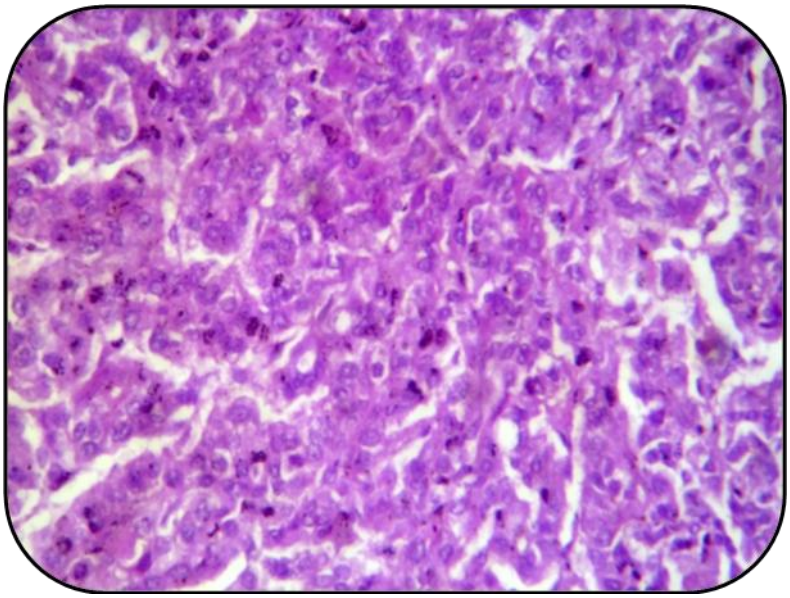


FIG 15: TUMOUR CELLS WITH ATYPIA & MITOSIS

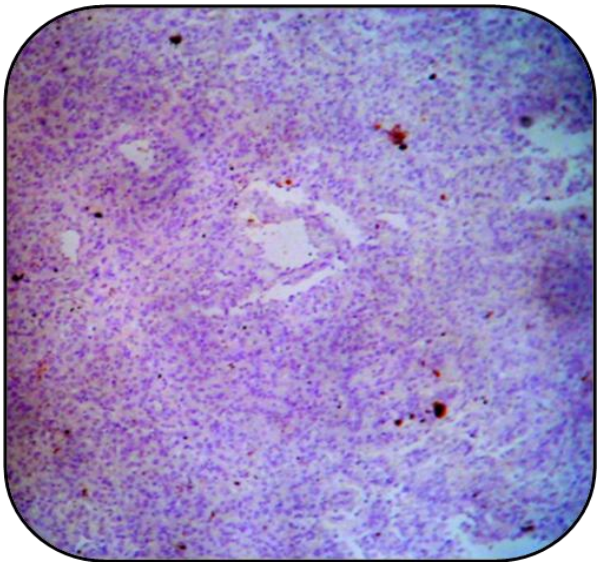


FIG 16: TUMOUR CELLS NEGATIVE FOR ALL IHC MARKERS

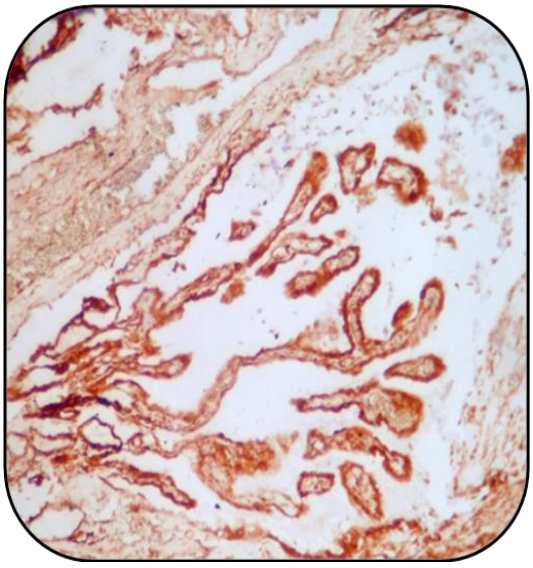


FIG 17: ADJACENT NORMAL CHOROID POSITIVE FOR CK

PAPILLARY MENINGIOMA

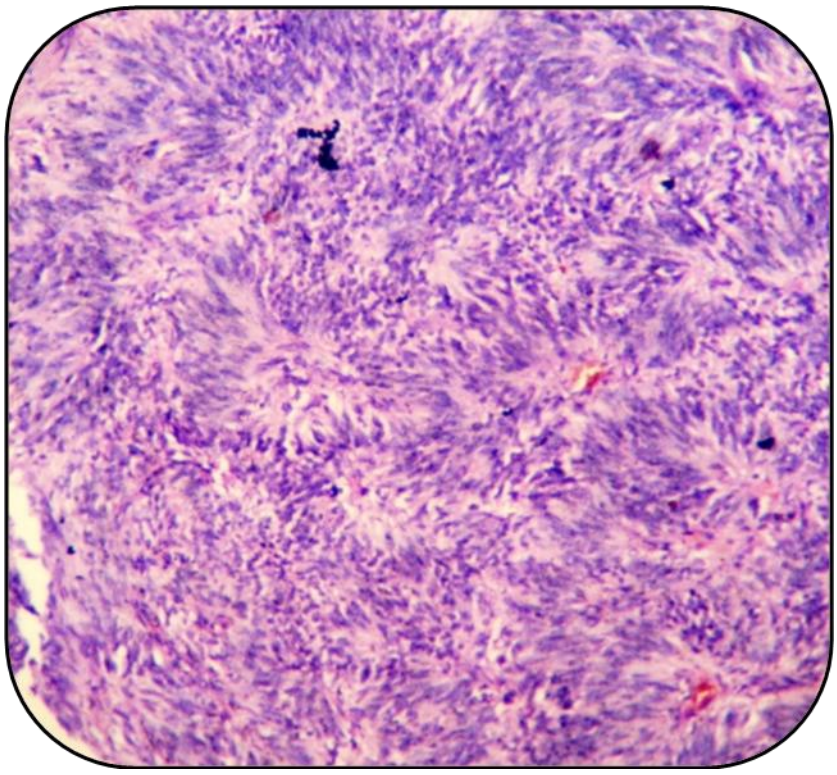


FIG 18 :PAPILLARY PATTERN WITH ELONGATED CELLS

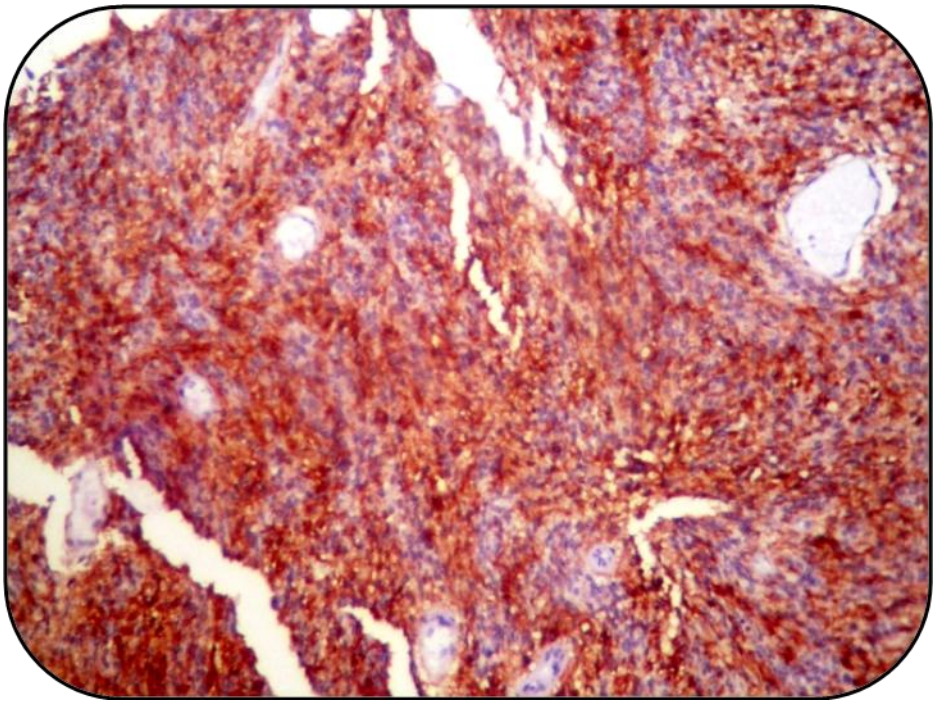


FIG 19: EMA- CYTOPLSMIC POSITIVITY IN TUMOUR CELLS

PAPILLARY MENINGIOMA

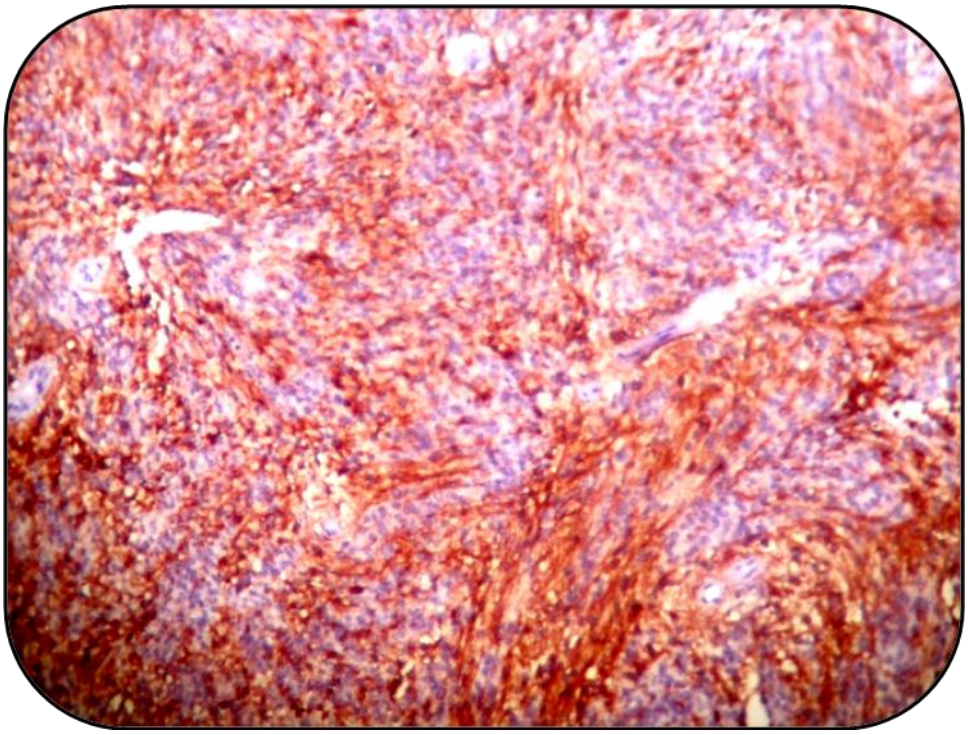


FIG 20: VIMENTIN – CYTOPLASMIC POSITIVITY IN TUMOUR CELLS

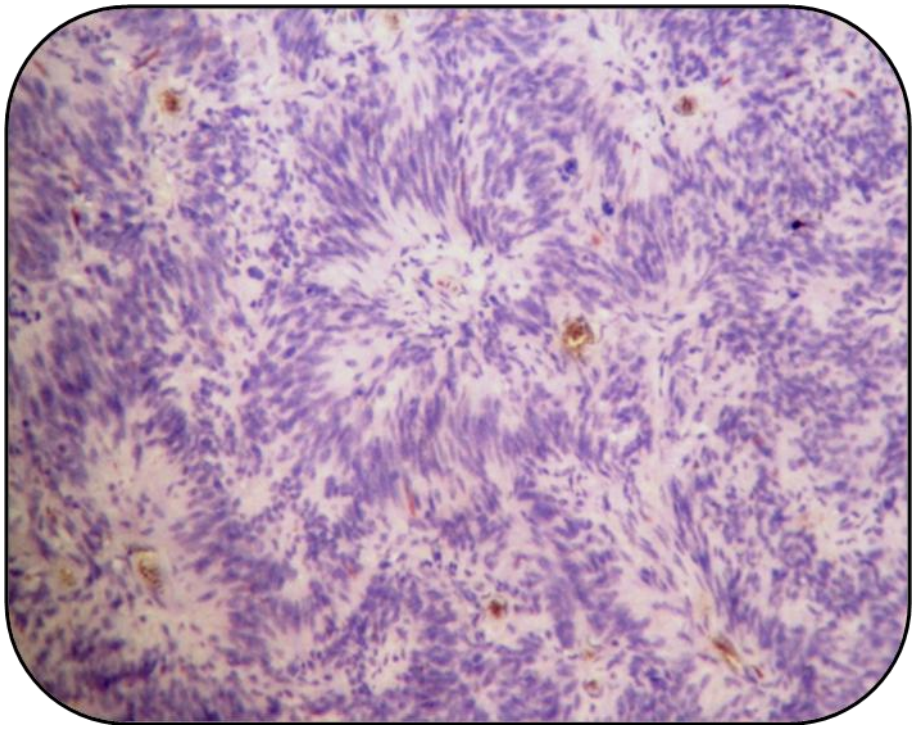


FIG 21: GFAP NEGATIVITY IN TUMOUR CELLS

PAPILLARY MENINGIOMA WITH RHABDOID DIFFERENTIATION

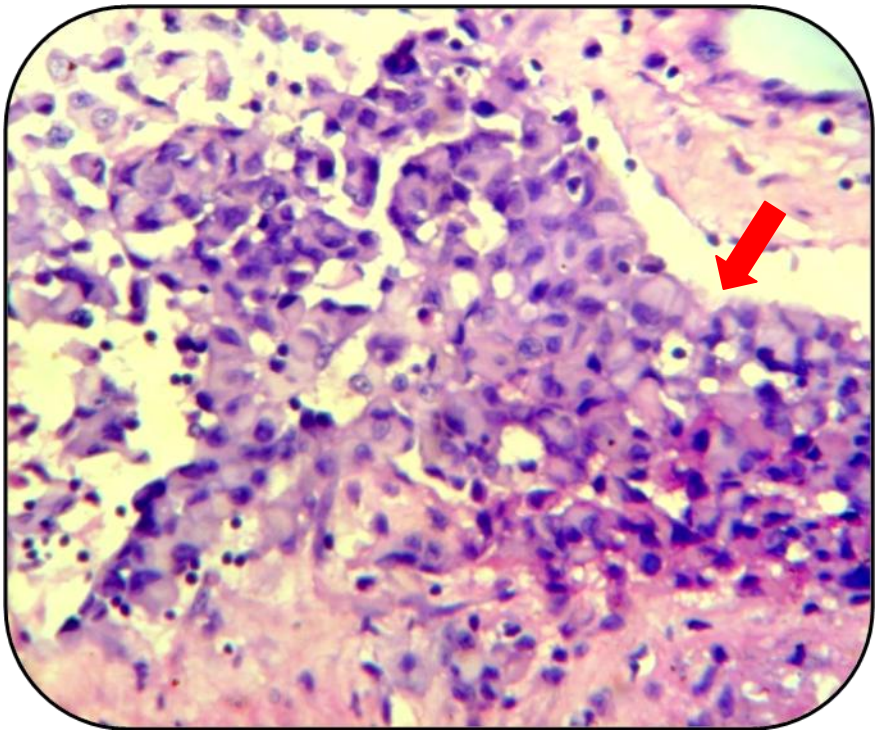


FIG 22: CELLS WITH RHABDOID MORPHOLOGY

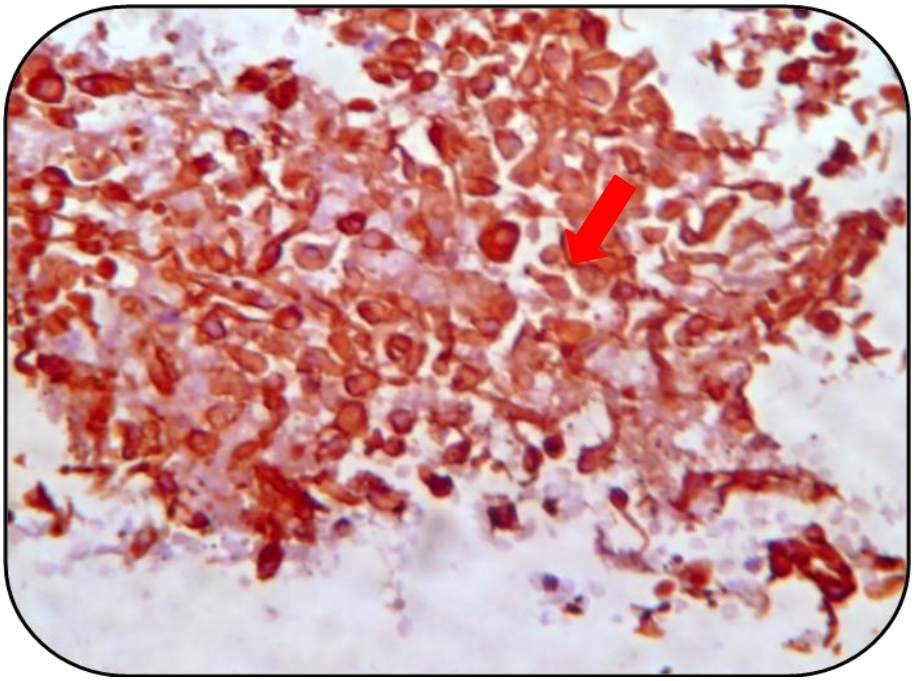


FIG 23: DESMIN – CYTOPLASMIC STRONG POSITIVITY IN CELLS WITH RHABDOID MORPHOLOGY

PAPILLARY MENINGIOMA WITH RHABDOID DIFFERENTIATION

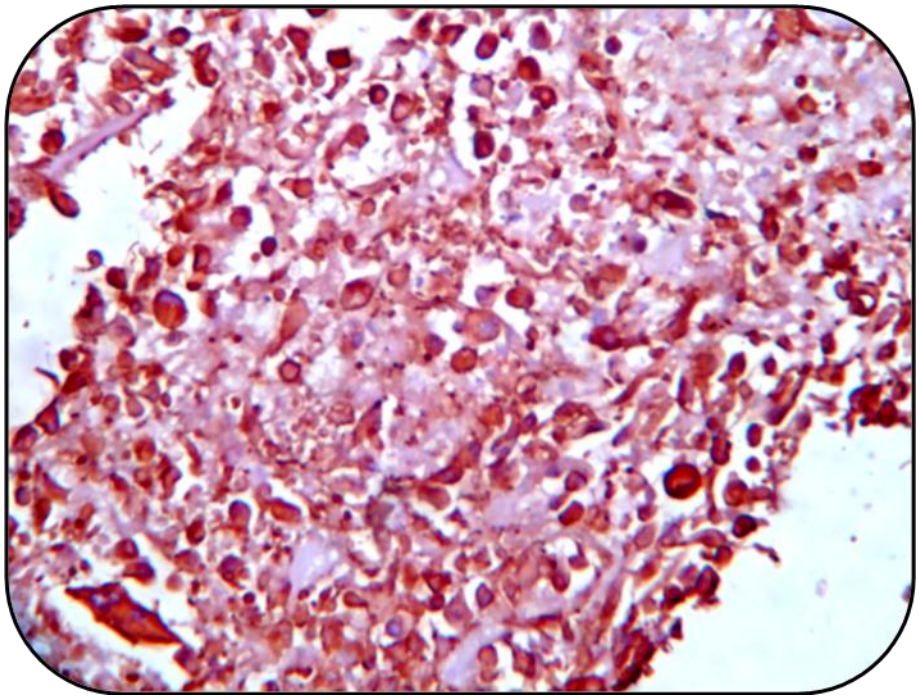


FIG 24: VIMENTIN – CYTOPLASMIC STRONG POSITIVITY IN CELLS WITH RHABDOID MORPHOLOGY

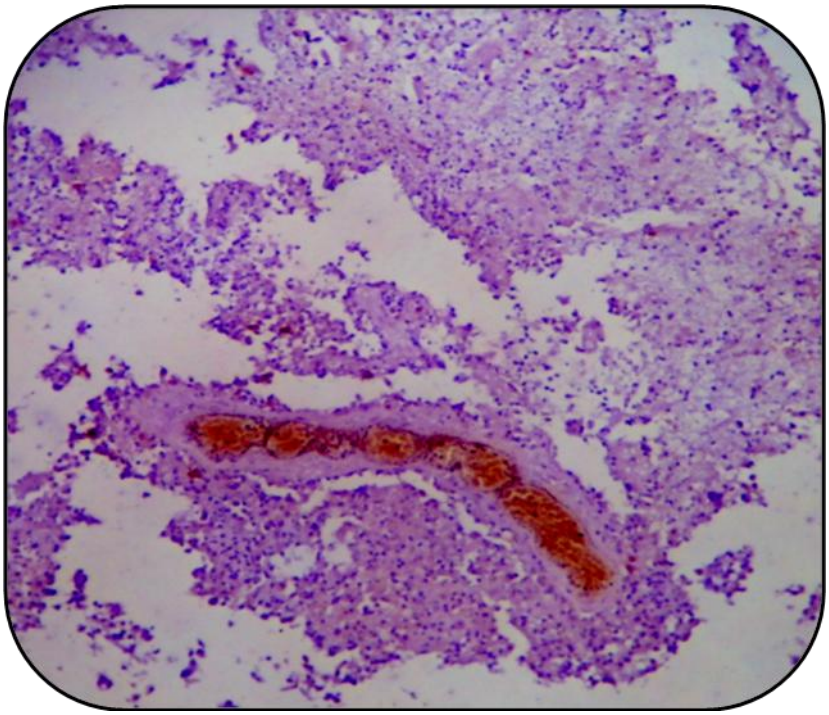


FIG 25: GFAP NEGATIVE IN TUMOUR CELLS

PAPILLARY VARIANT OF CRANIOPHARYNGIOMA

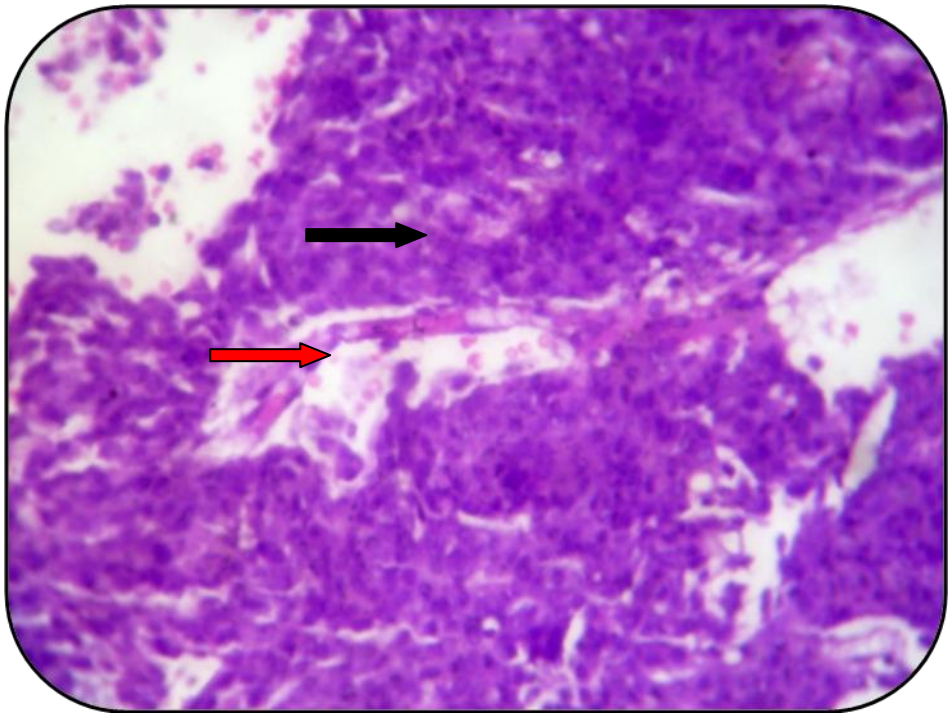


FIG 26: CENTRAL BLOOD VESSEL CORE (RED) LINED BY TUMOUR CELLS (PAPILLARY PATTERN)(BLACK)

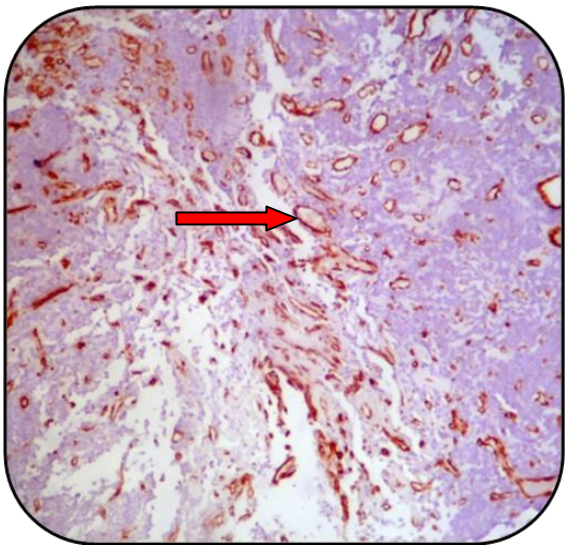


FIG 27: VIMENTIN POSITIVITY IN CENTRAL BLOOD VESSEL CORE (RED)

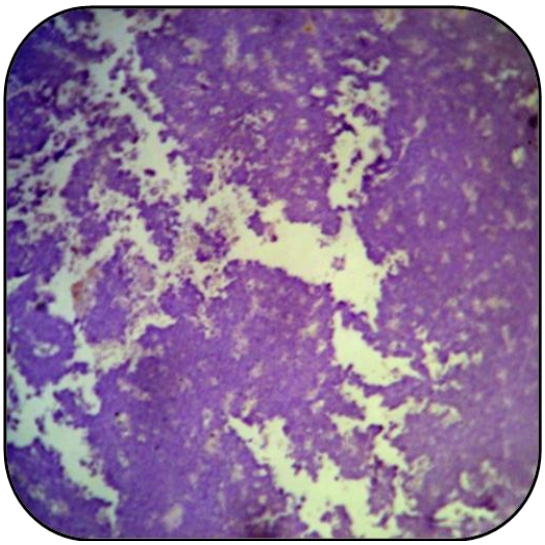


FIG 28: ALL OTHER MARKERS- NEGATIVE

EPENDYMOBLASTOMA

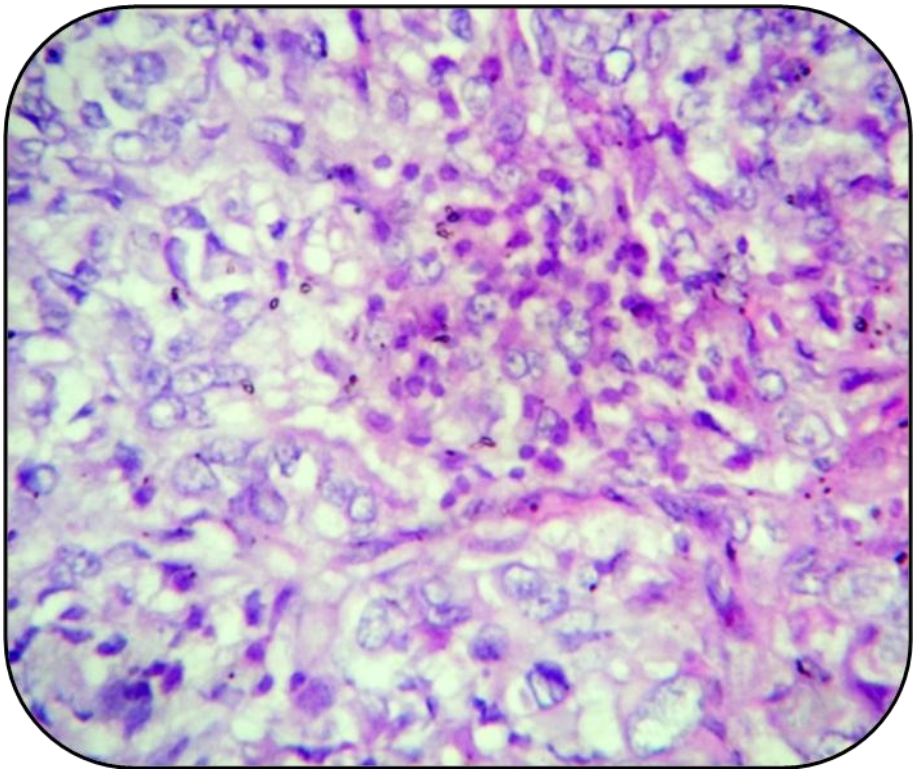


FIG 29: DENSE CELLULARITY WITH THIN WALLED BLOOD VESSEL

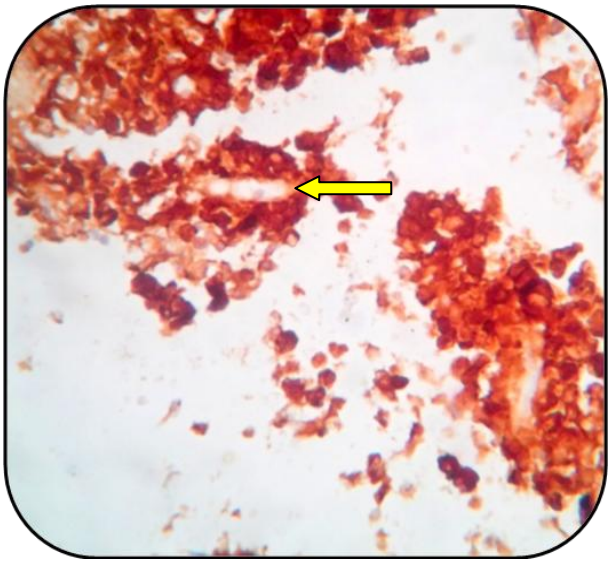


FIG 30 & 31: GFAP & S-100 POSITIVITY IN EPENDYMOBLASTOMATOUS ROSETTES (YELLOW)

METASTATIC DEPOSITS FROM LUNG CARCINOMA

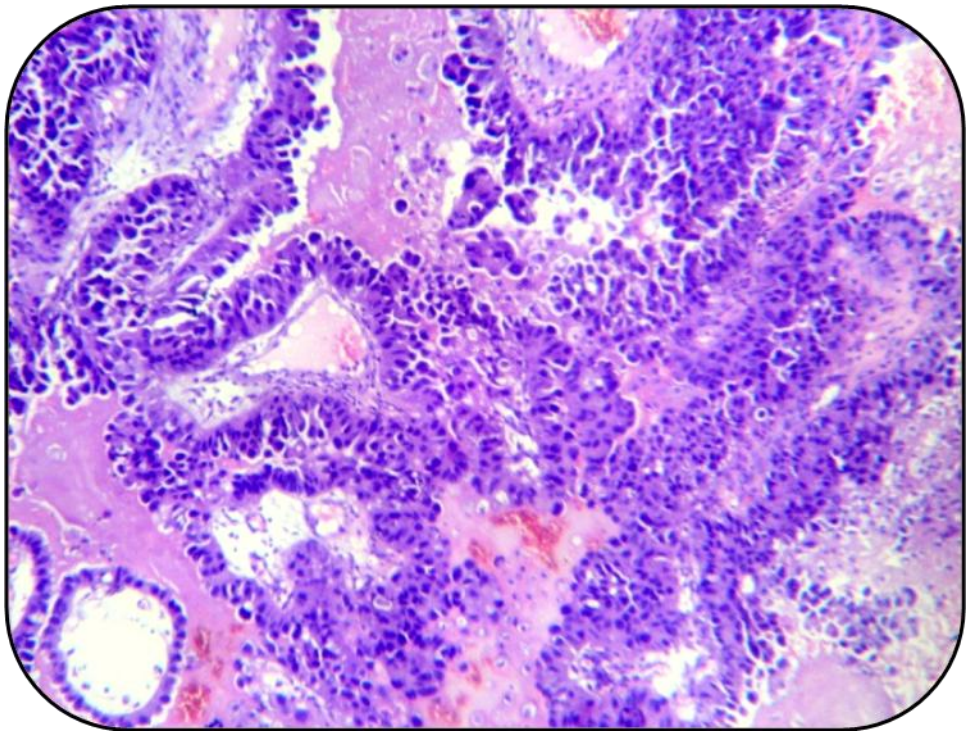


FIG 32: PAPILLARY PATTERN, HOBNAIL PATTERN OF CELLS, HYPERCHROMATIC NUCLEI

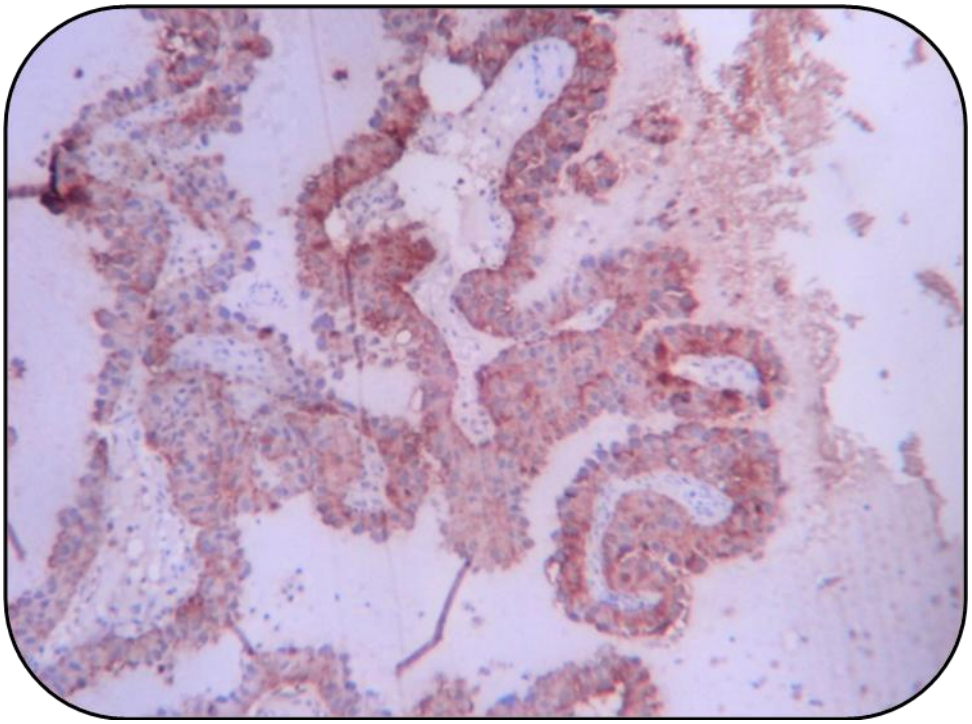


FIG 33: CK- CYTOPLASMIC STRONG POSITIVITY IN TUMOUR CELLS

METASTATIC DEPOSITS FROM LUNG CARCINOMA

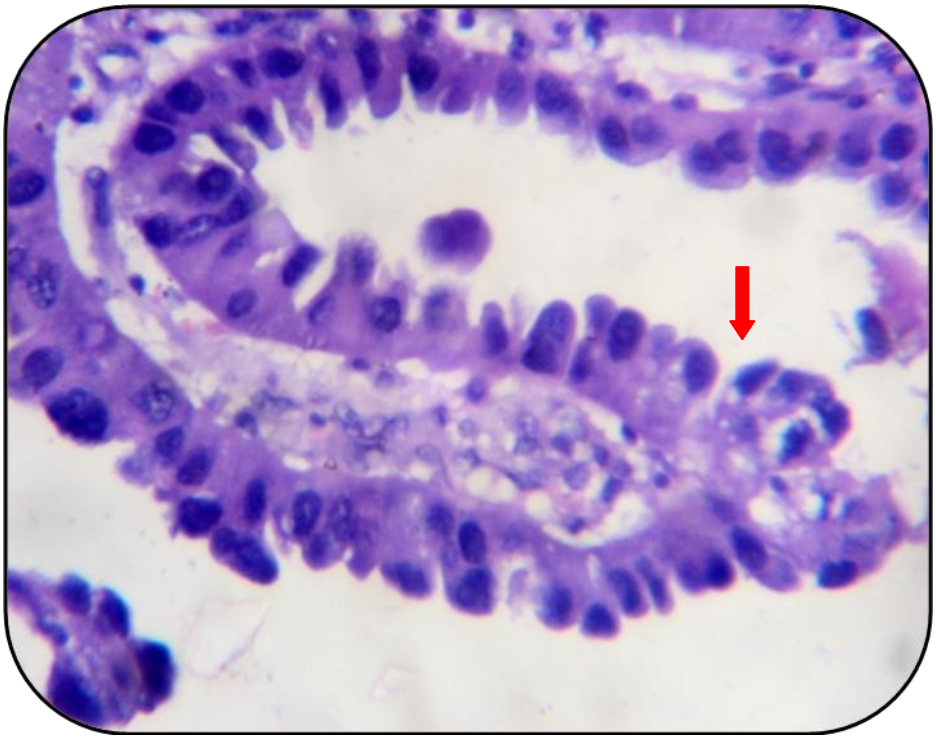


FIG 34: HOBNAIL PATTERN OF CELLS (RED) HYPERCHROMATIC NUCLEI

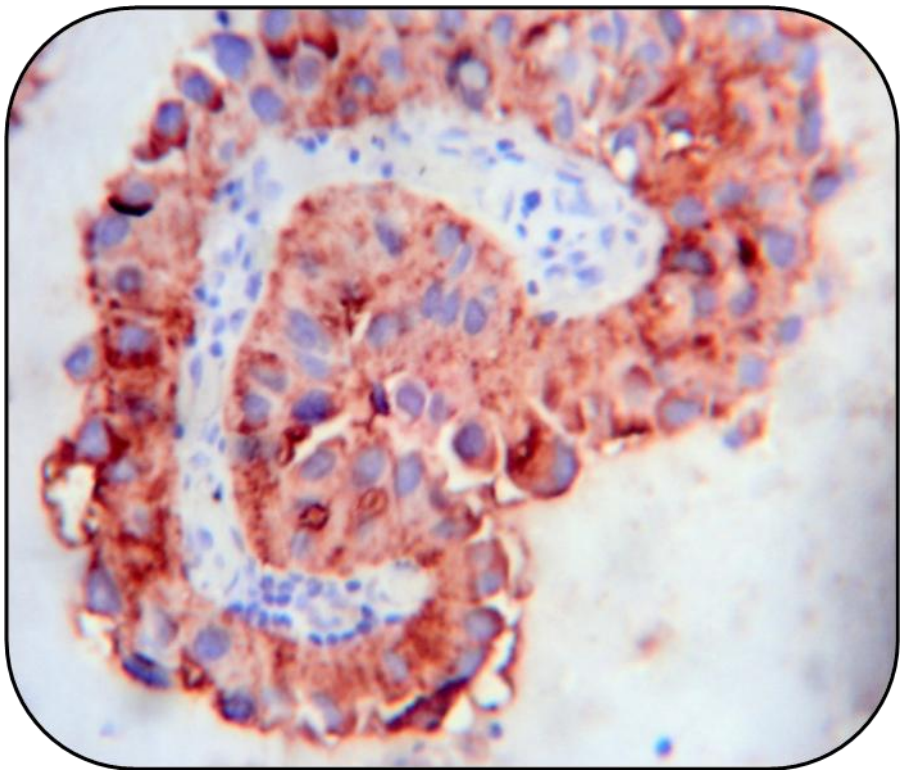


FIG 35: CEA- CYTOPLASMIC & MEMBRANOUS POSITIVITY IN TUMOUR CELLS

METASTATIC PAPILLARY ADENO CARCINOMA DEPOSITS FROM UNKNOWN PRIMARY

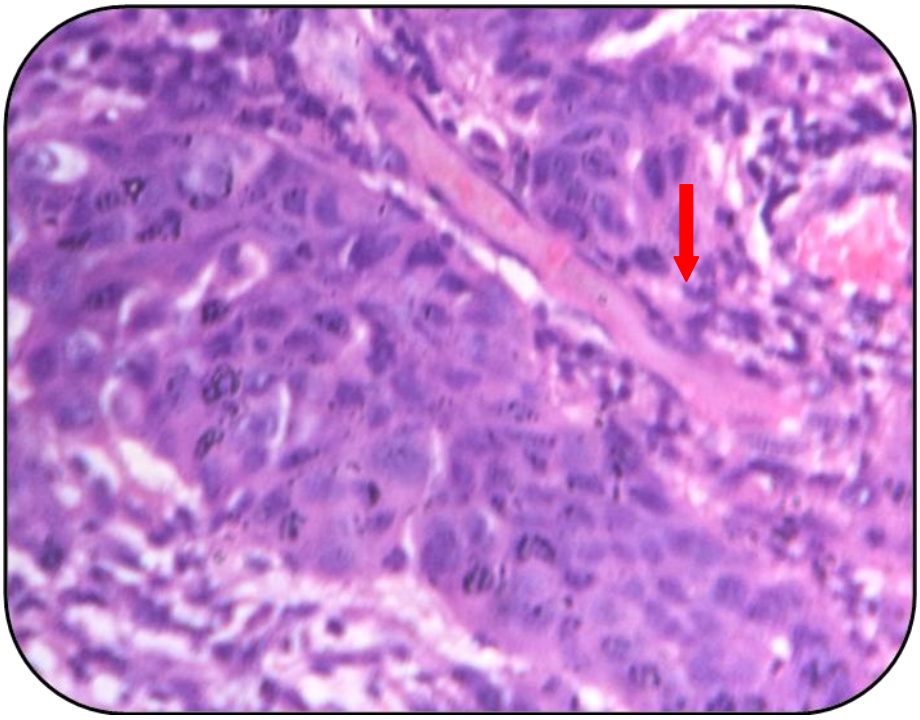


FIG 36: PAPILLARY PATTERN (RED) WITH HYPERCHROMATIC NUCLEI

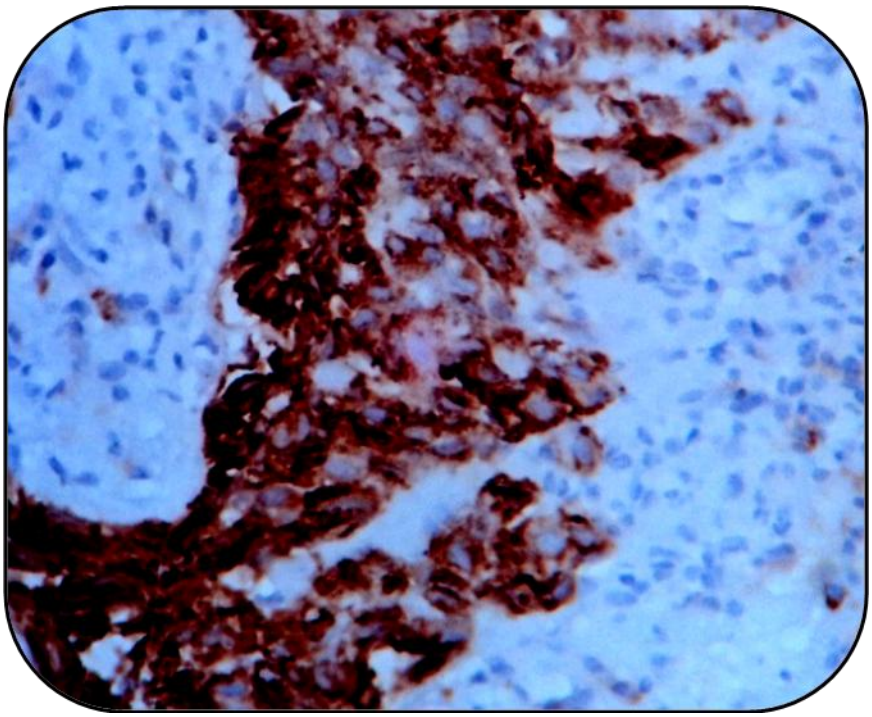


FIG 37: CK- STRONG CYTOPLASMIC & MEMBRANOUS POSITIVITY

METASTATIC PAPILLARY ADENO CARCINOMA DEPOSITS FROM UNKNOWN PRIMARY

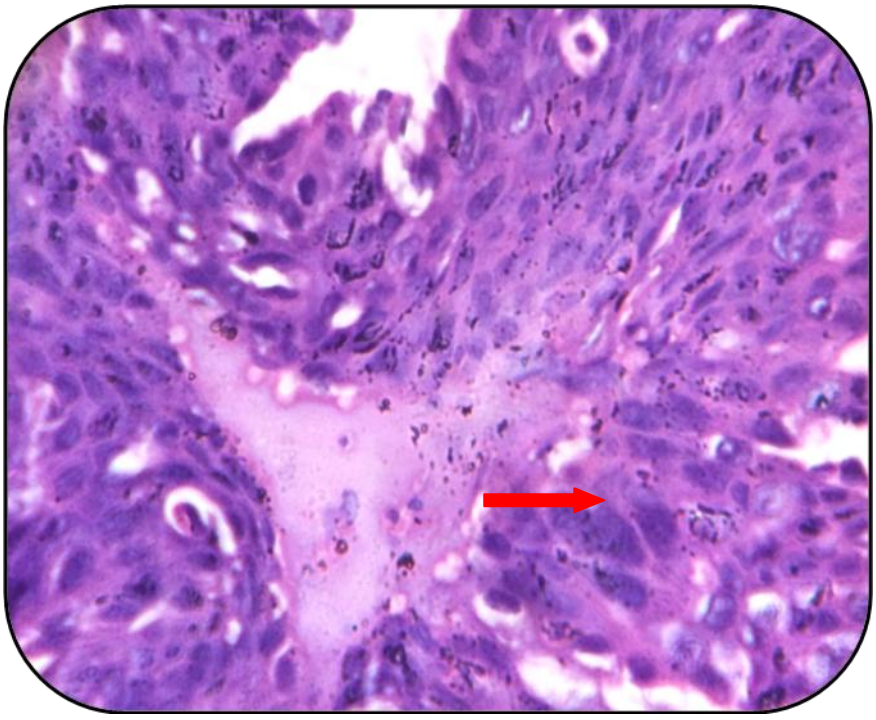


FIG 38: PAPILLARY PATTERN (RED) WITH HYPERCHROMATIC PLEOMOPHIC NUCLEI

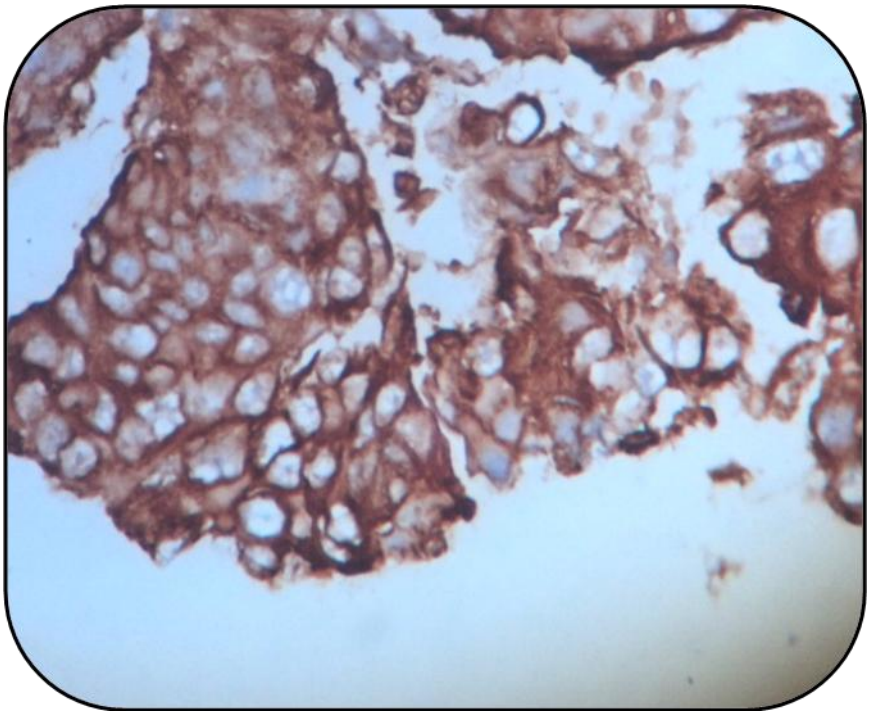


FIG 39: CEA- STRONG CYTOPLASMIC & MEMBRANOUS POSITIVITY IN TUMOUR CELLS

METASTATIC DEPOSTS FROM THYROID CARCINOMA

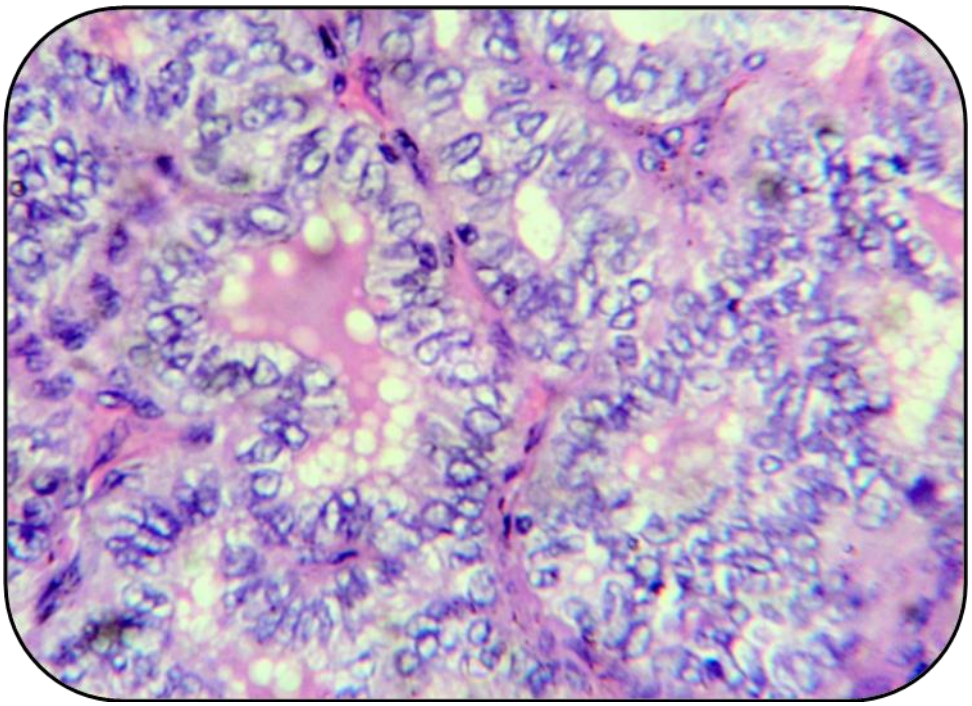


FIG 40: PAPILLARY CARCINOMA THYROID METASTASIS

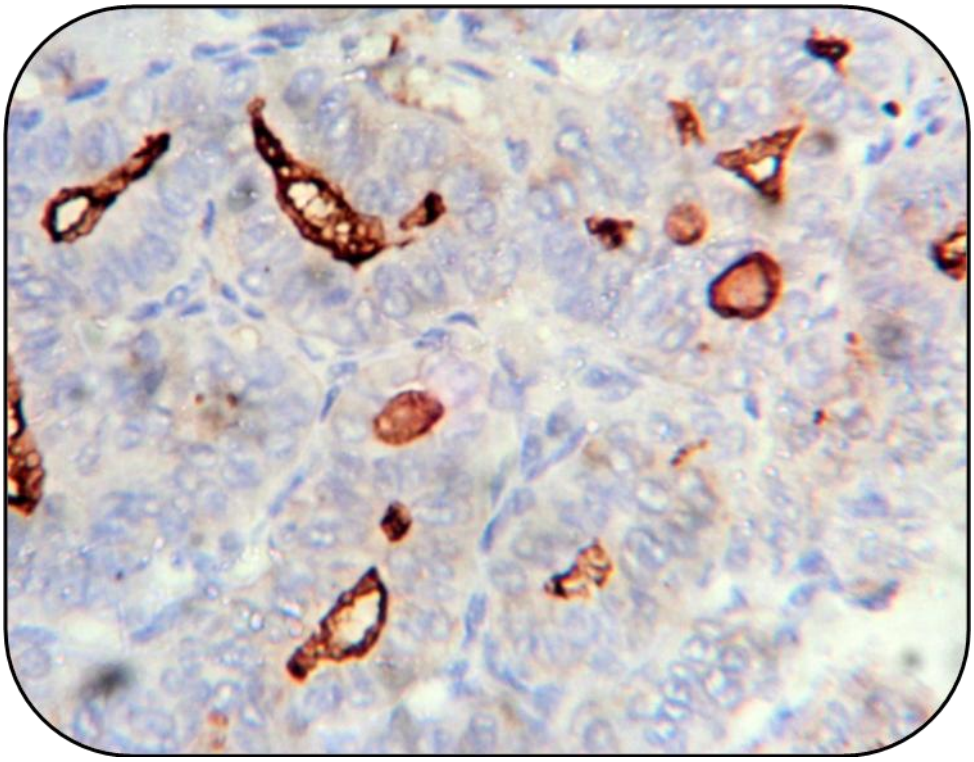


FIG 41: THYROGLOBULIN POSITIVITY IN COLLOID

METASTATIC DEPOSTS FROM OVARIAN CARCINOMA

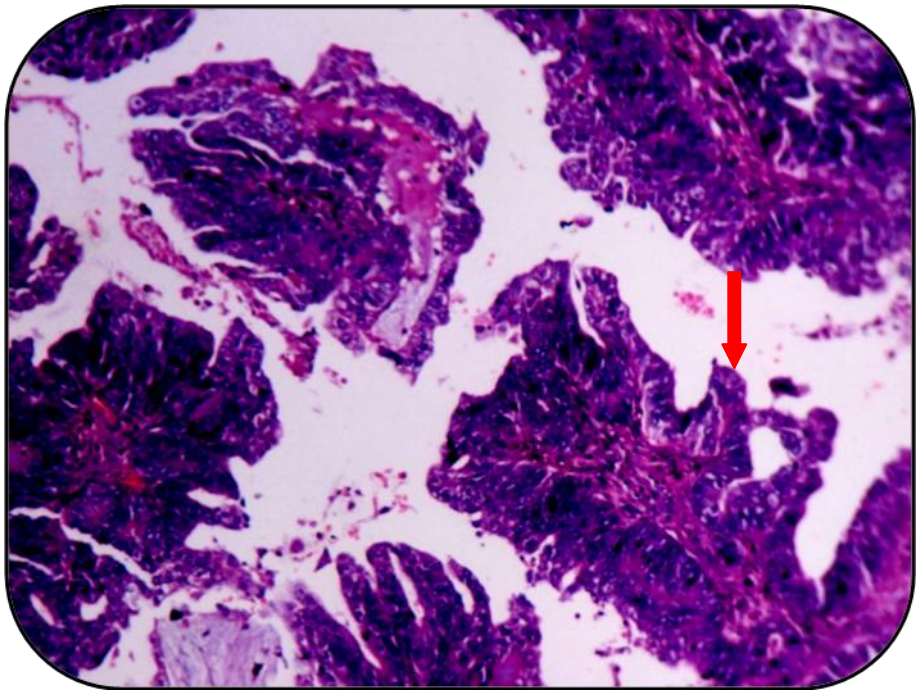


FIG 42: PAPILLARY PATTERN (RED), STRATIFICATION OF NUCLEI, HYPERCHROMATIC NUCLEI

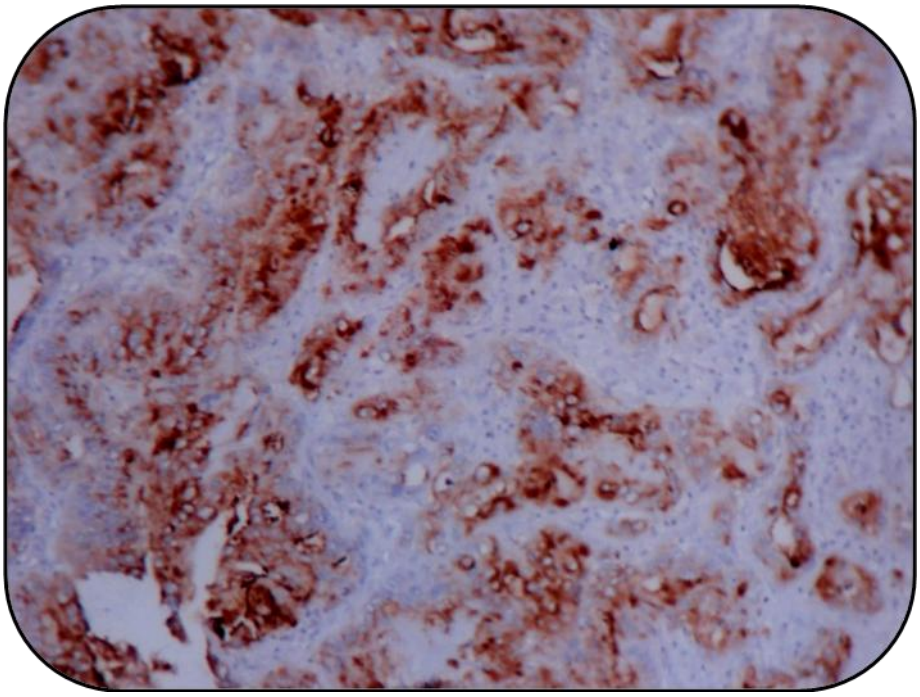


FIG 43: CK- CYTOPLASMIC POSITIVITY IN TUMOUR CELLS

METASTATIC DEPOSTS FROM OVARIAN CARCINOMA

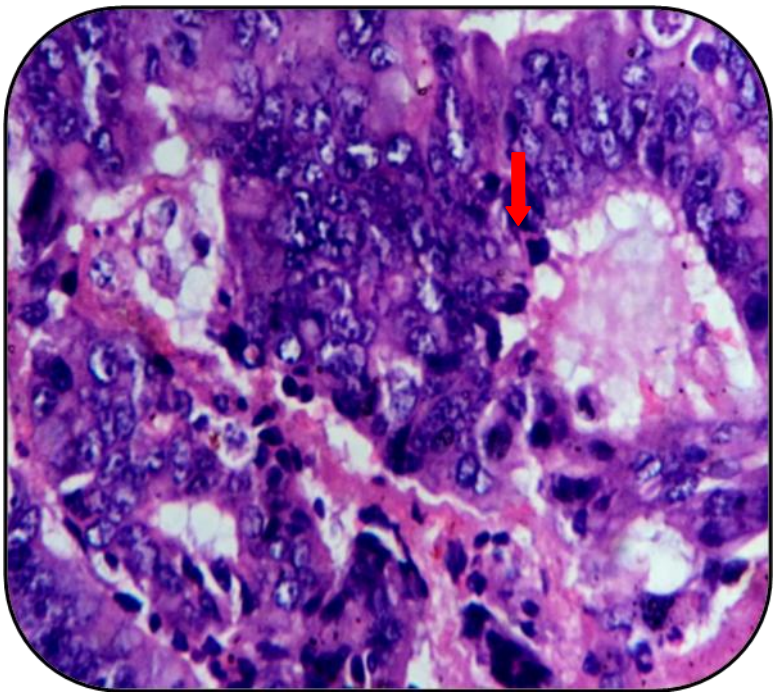


FIG 44: PAPILLARY PATTERN (RED), STRATIFICATION OF NUCLEI, HYPERCHROMATIC NUCLEI

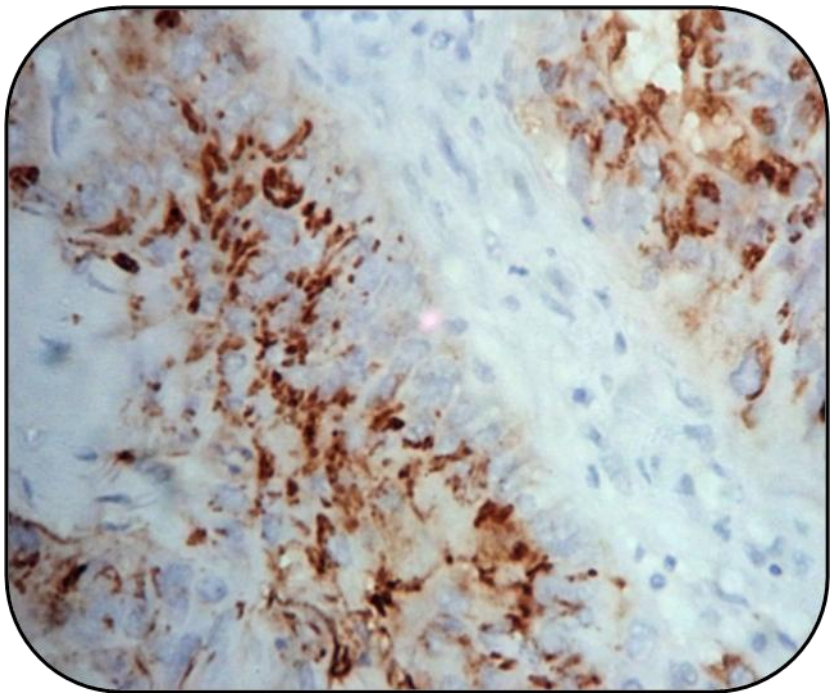


FIG 45: CEA – APICAL CYTOPLASMIC POSITIVITY IN TUMOUR CELLS

METASTATIC PAPILLARY ADENO CARCINOMA DEPOSITS FROM UNKNOWN PRIMARY

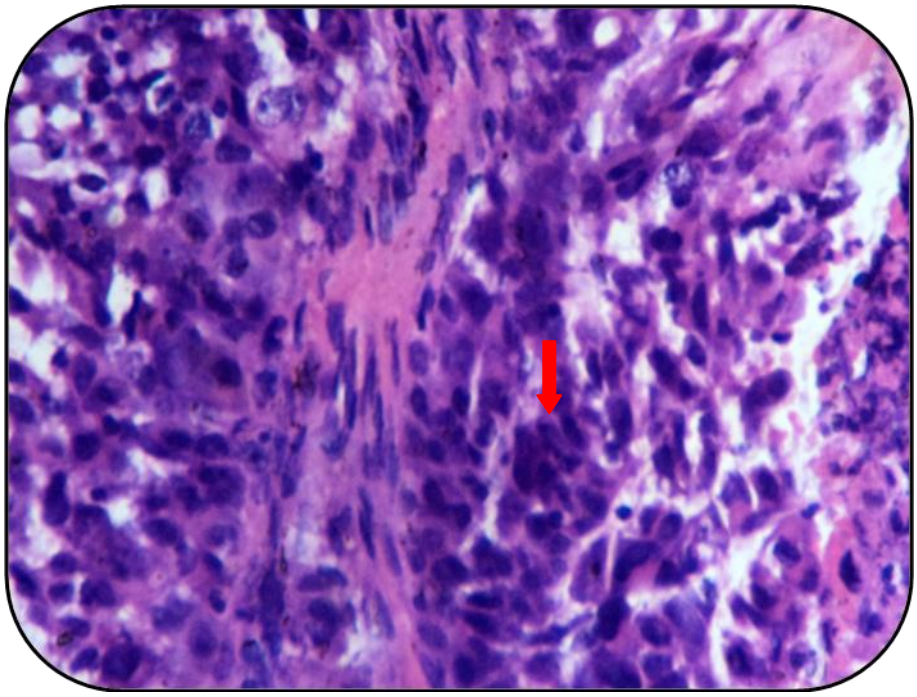


FIG 46: PAPILLARY PATTERN (RED), STRATIFICATION OF NUCLEI, HYPERCHROMATIC NUCLEI

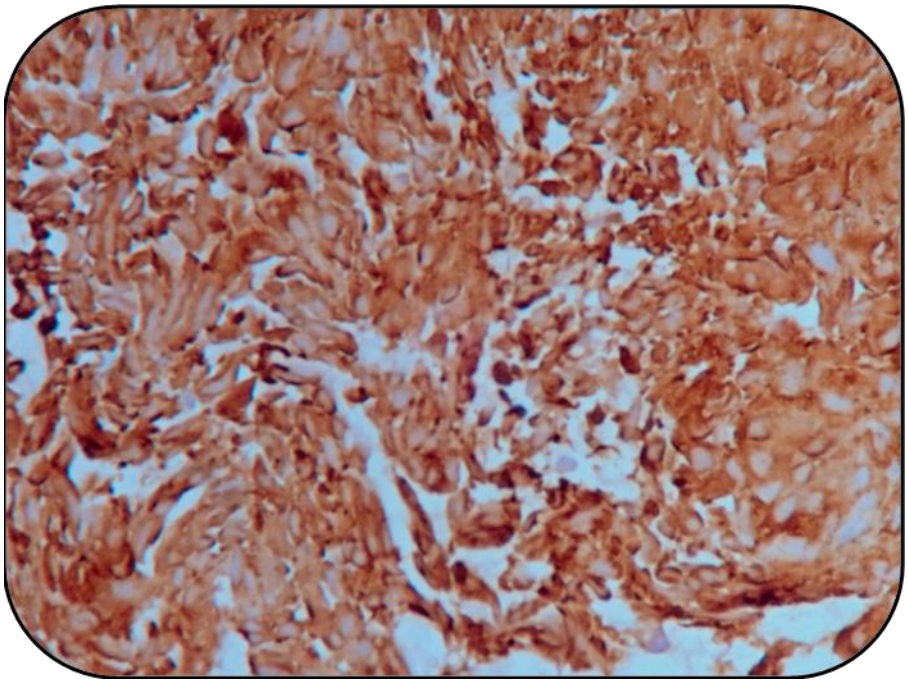


FIG 47: CK- STRONG CYTOPLASMIC POSITIVITY IN TUMOUR CELLS

METASTATIC PAPILLARY ADENO CARCINOMA DEPOSITS FROM UNKNOWN PRIMARY

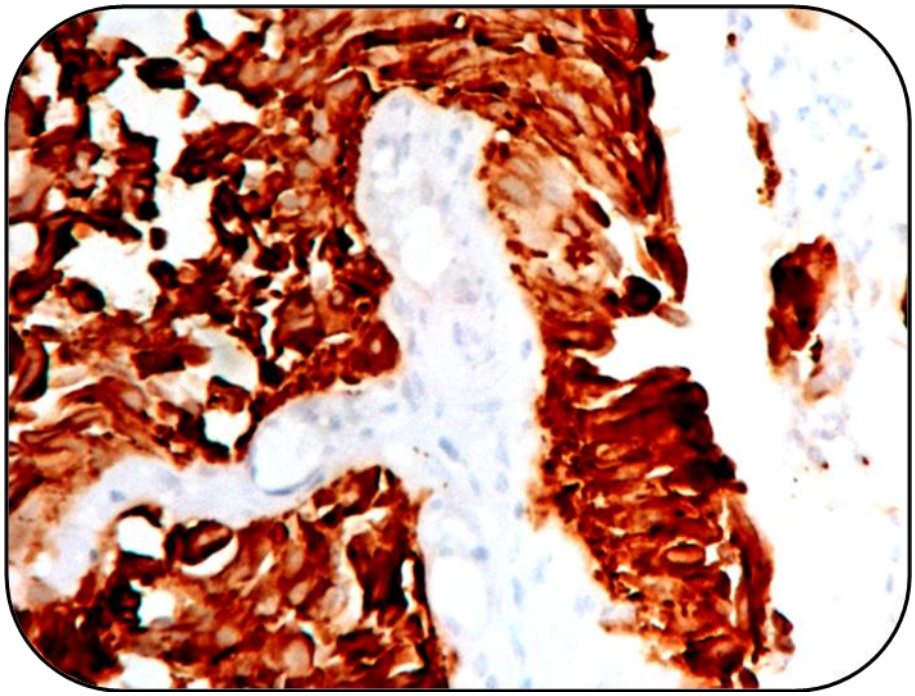


FIG 48: CEA- STRONG CYTOPLASMIC & MEMBRANOUS POSITIVITY IN TUMOUR CELLS

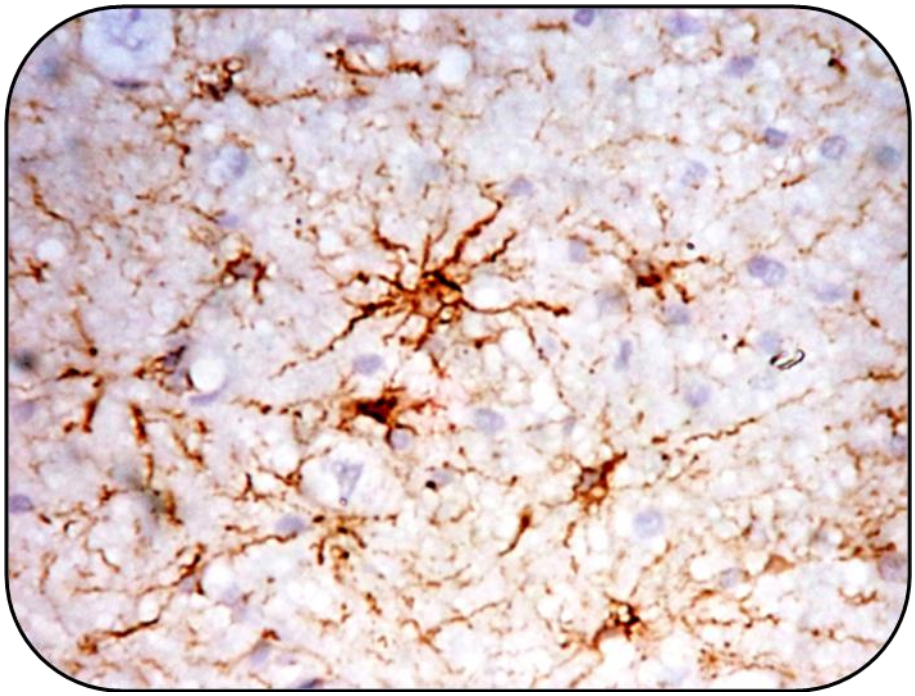


FIG 49: GFAP –POSITIVITY IN NORMAL ASTROCYTES

ABSTRACT

TITLE: INCIDENCE OF PAPILLARY NEOPLASMS OF NERVOUS SYSTEM IN A TERTIARY CARE HOSPITAL. ROLE OF IMMUNOHISTOCHEMISTRY IN THEIR DIFFERENTIAL DIAGNOSIS AND CLASSIFICATION

INTRODUCTION:

- Nervous system neoplasms are common neoplasm affecting both adults and children. Incidence, prevalence and survival rates are important to know the burden of disease among different populations. Often the histological appearance alone cannot conclude the diagnosis. In difficult cases use of immunohistochemistry aid in differentiating metastasis from primary tumour, histological sub typing and grading. In this study we analysed the data from our tertiary care hospital to find the epidemiology of papillary neoplasms of nervous system, histopathology, and employed immunohistochemistry to differentiate each tumour.

AIMS AND OBJECTIVES:

1. To study the incidence of papillary neoplasms of nervous system.
2. To study the immunohistochemical expression in primary nervous system tumours.

RESULTS:

- In a study period of 5 years, 62 cases of nervous system tumours with papillary pattern were subjected to histological and Immunohistochemical analysis to find out the usefulness of IHC in their diagnosis and differential diagnosis. The findings were correlated with WHO grading and analysis.

- Metastatic tumours with papillary pattern constituted 62.90% and this formed the most common tumours of nervous system. The peak age group was between 51 to 60 years with relative percentage of 20.97%.

CONCLUSION:

- The incidence of papillary neoplasms of nervous system in this study was 2.66%.

- Metastatic deposits with papillary pattern constituted a higher percentage and older age group has higher incidence similar to western population.

- Lung carcinoma producing brain metastasis constituted higher incidence similar to western population.

- In younger age group most of the papillary tumours were choroid plexus tumours.

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